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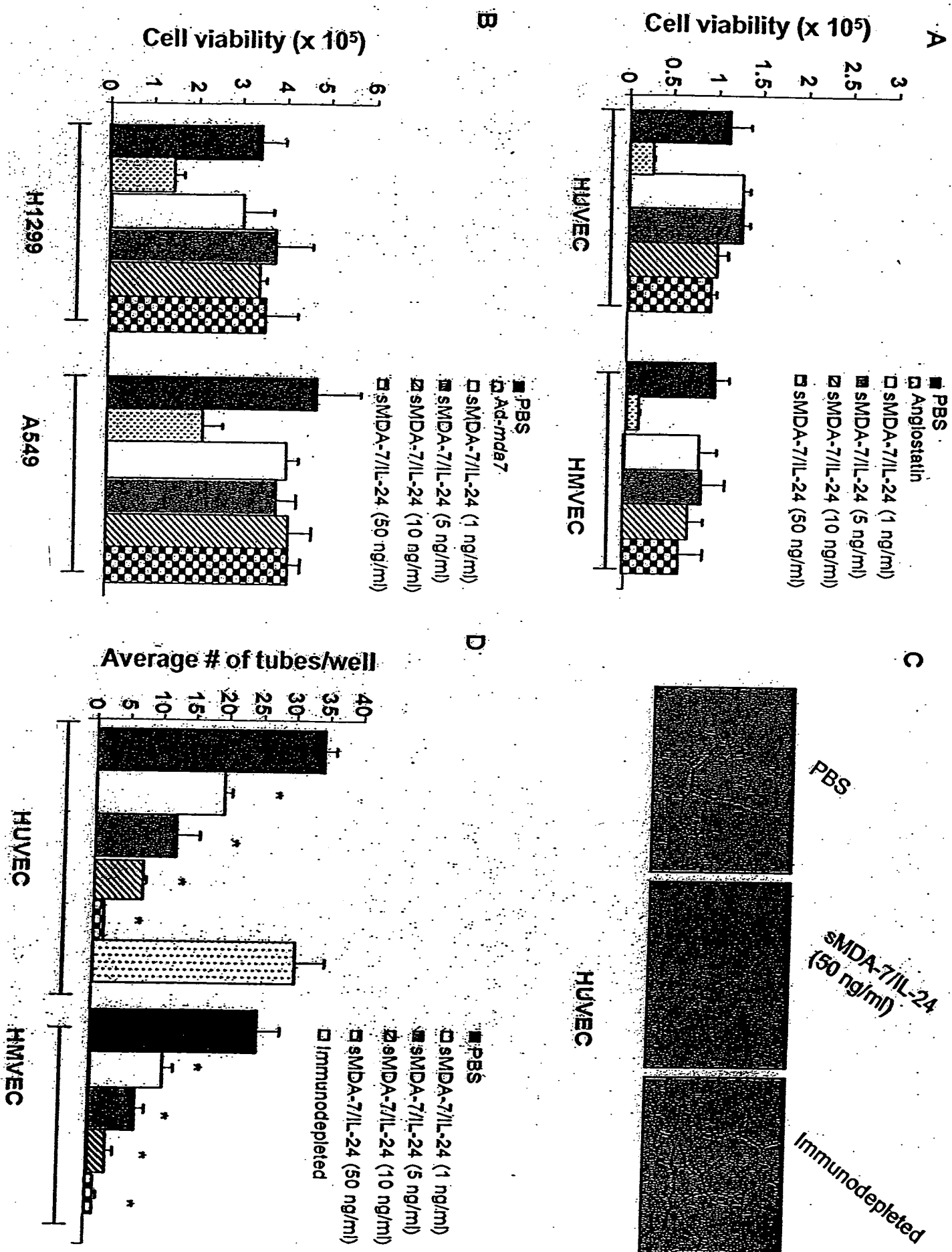
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FIG. 1



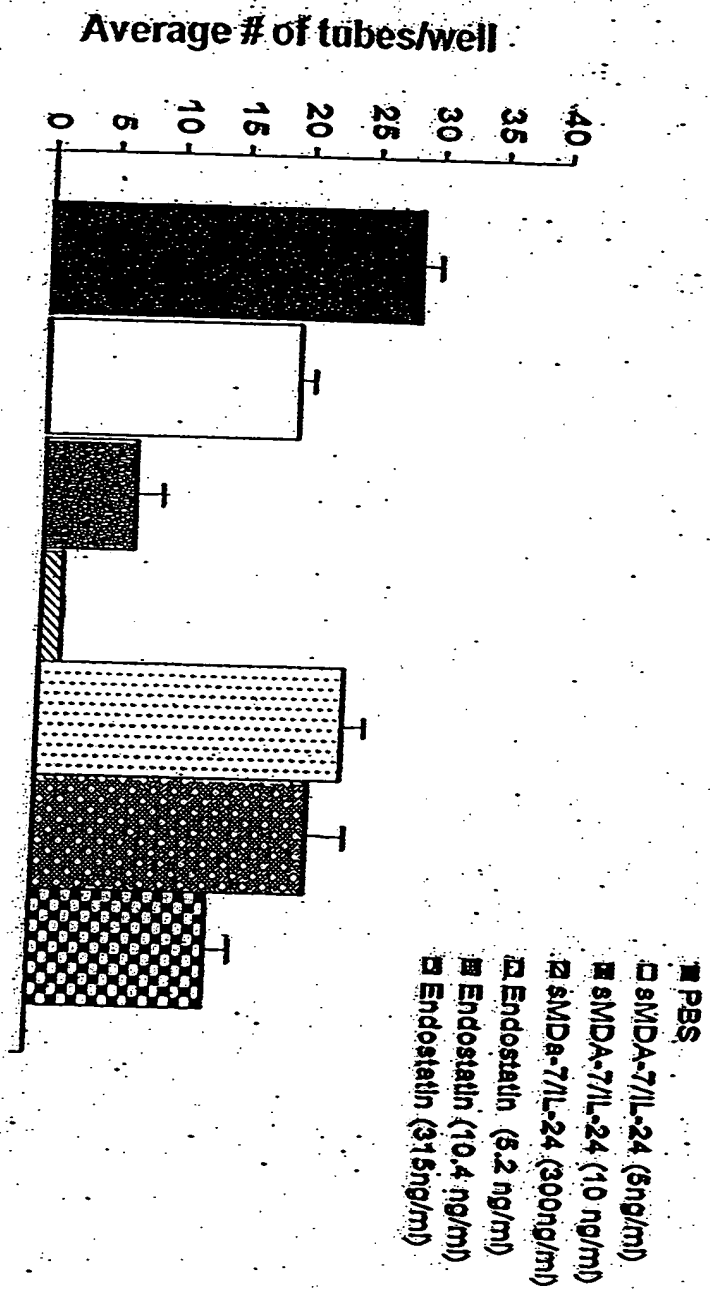
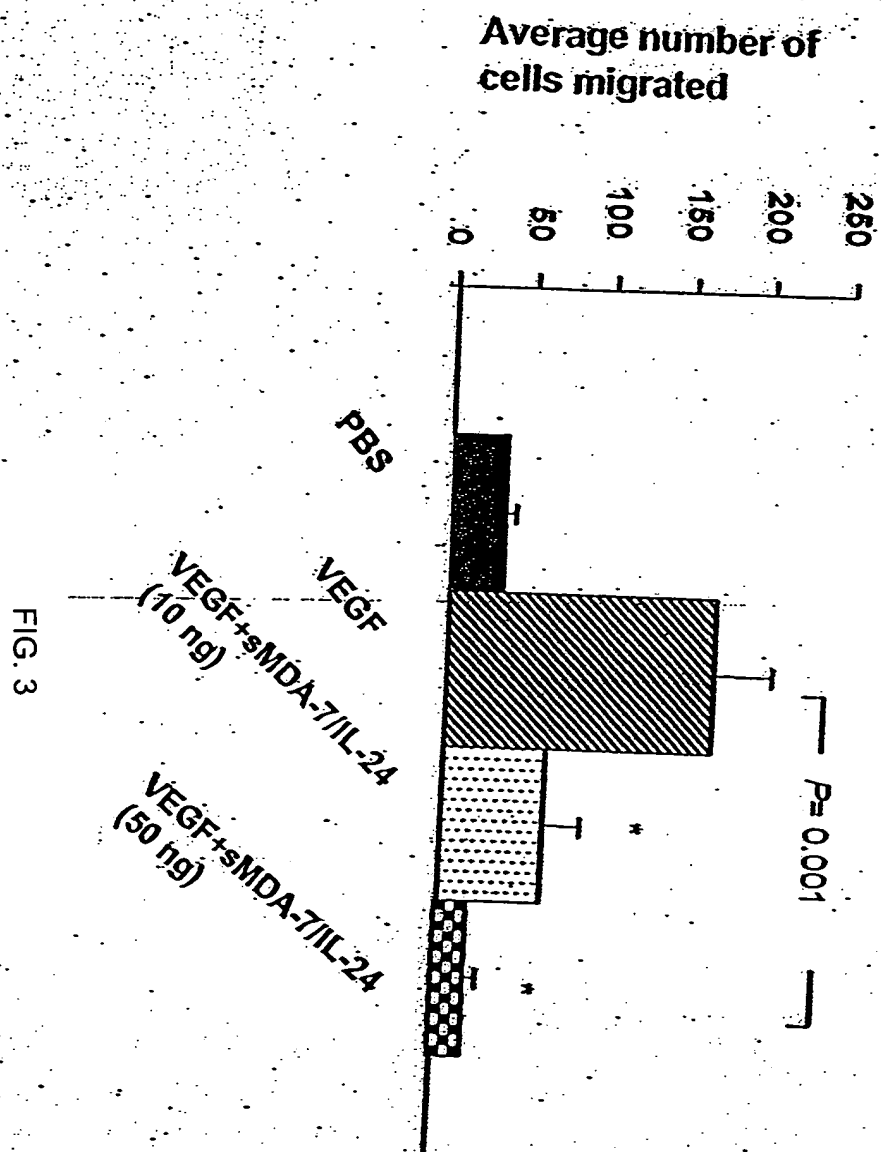


FIG. 2



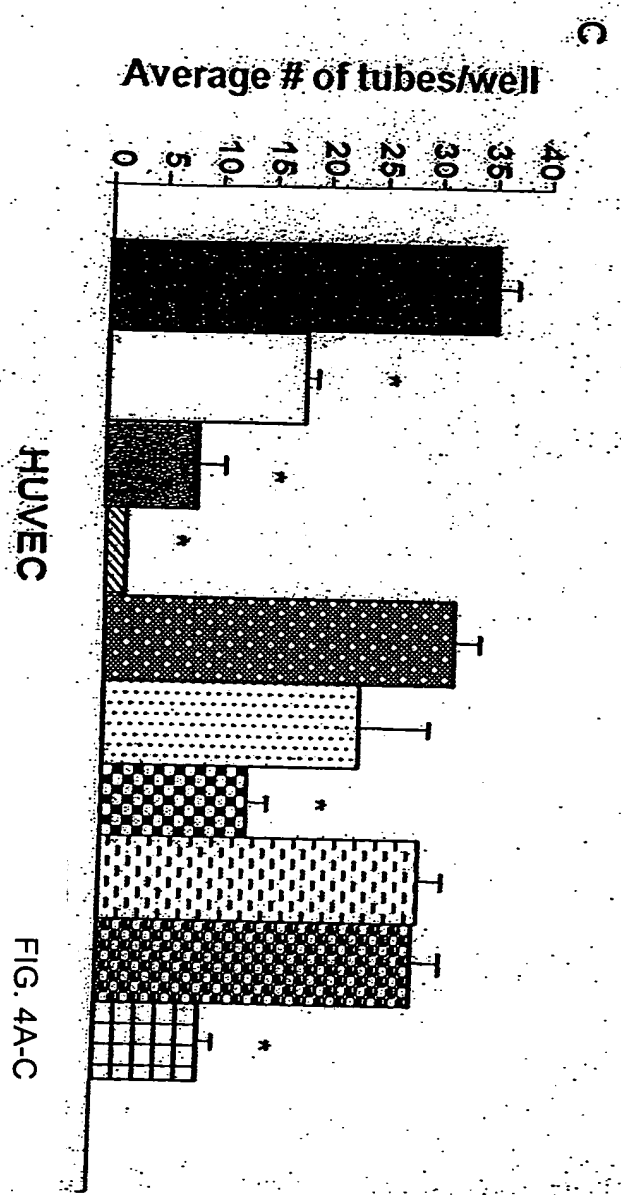
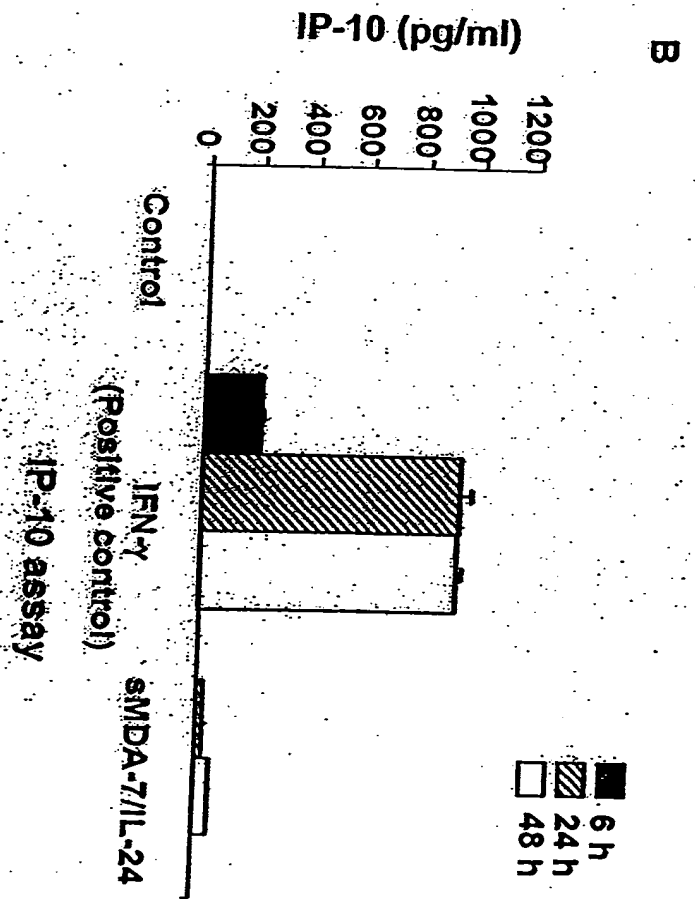
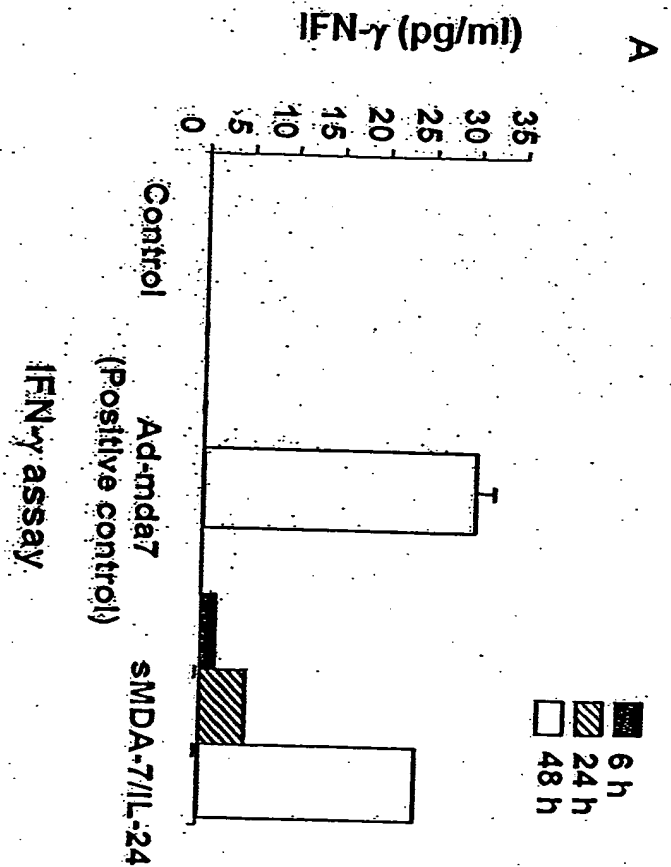
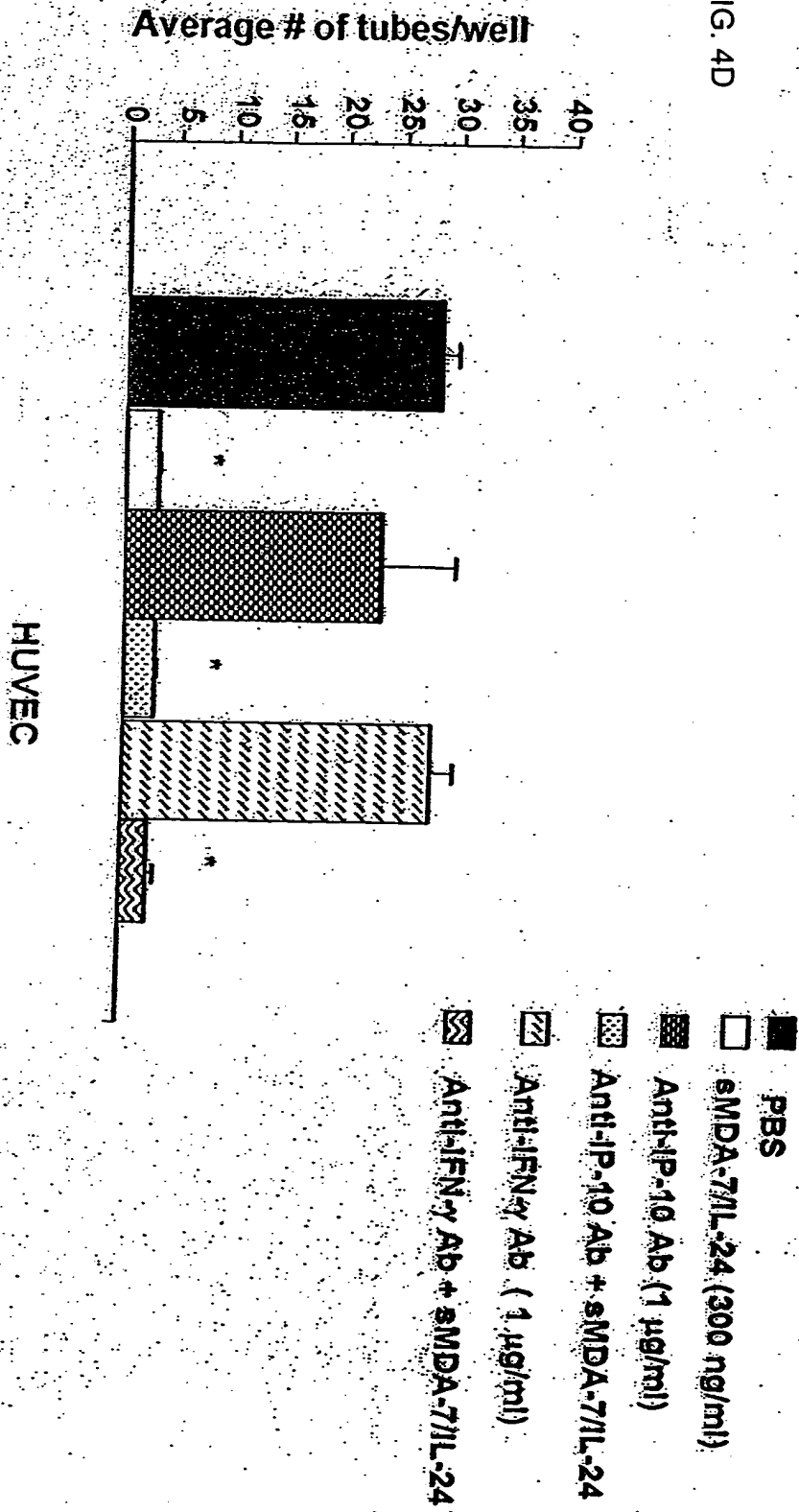


FIG. 4A-C

FIG. 4D



Average # of tubes/well

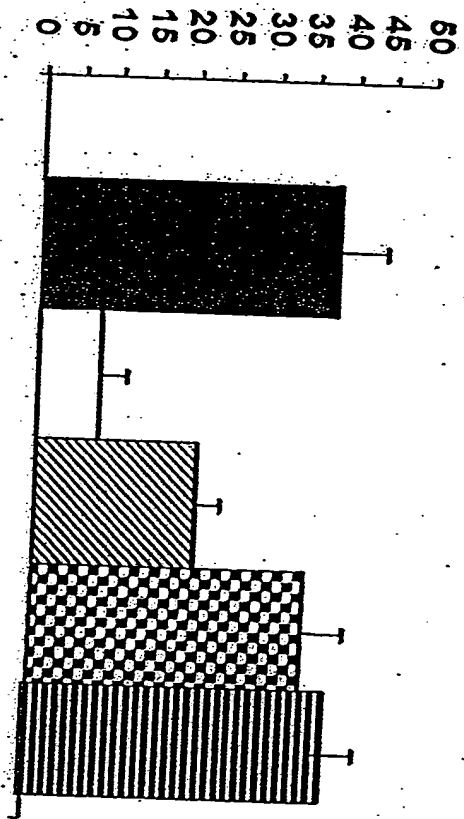
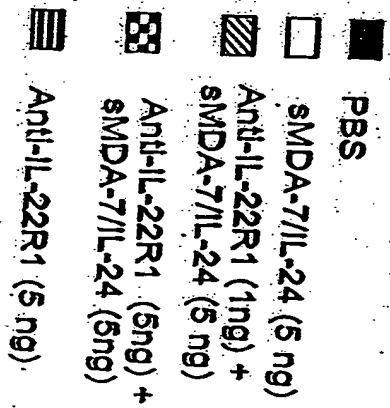


FIG. 5A



Average # of tubes/well

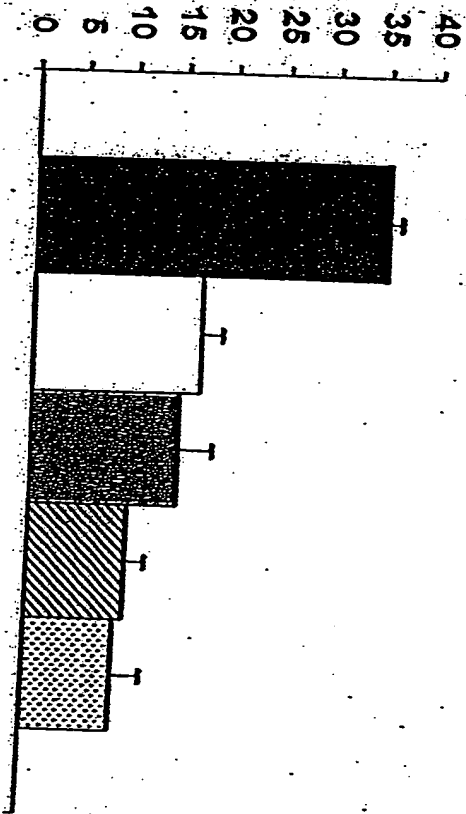
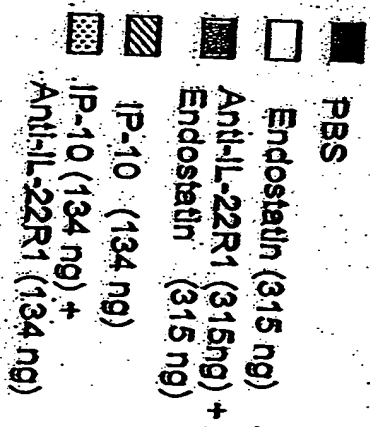


FIG. 5B



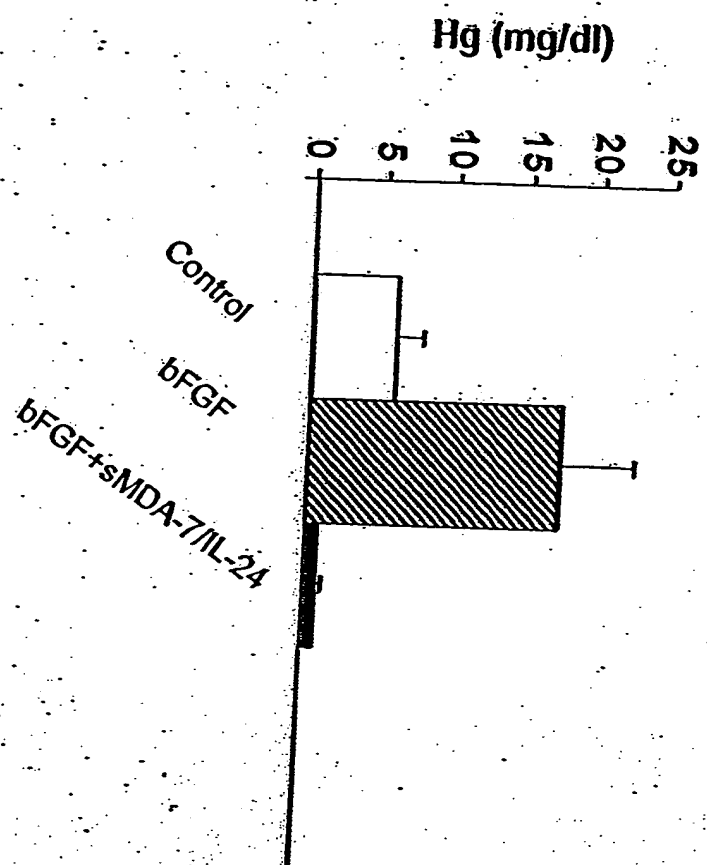


FIG. 6A

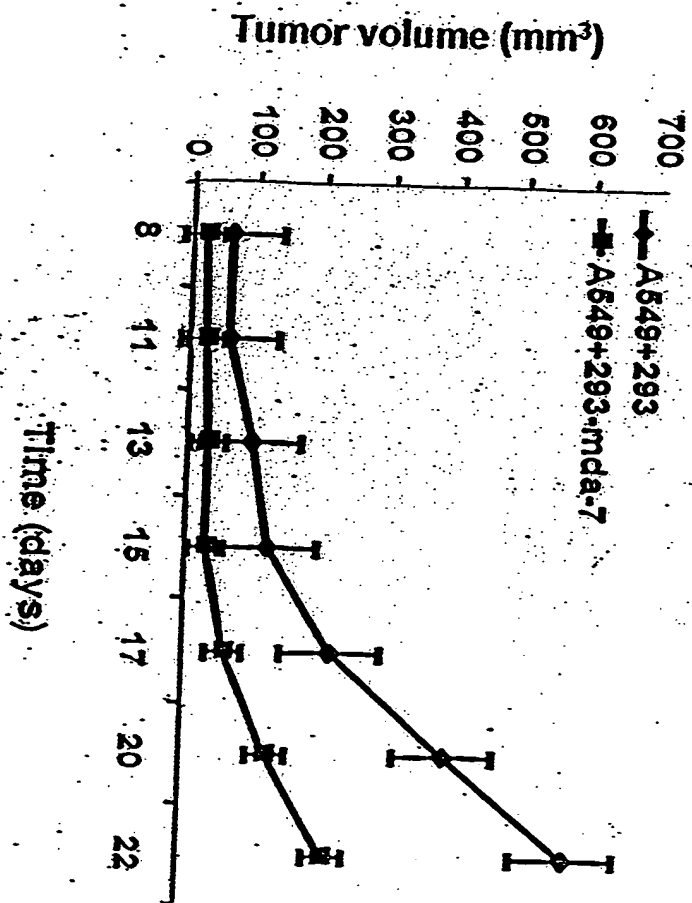


FIG. 6B

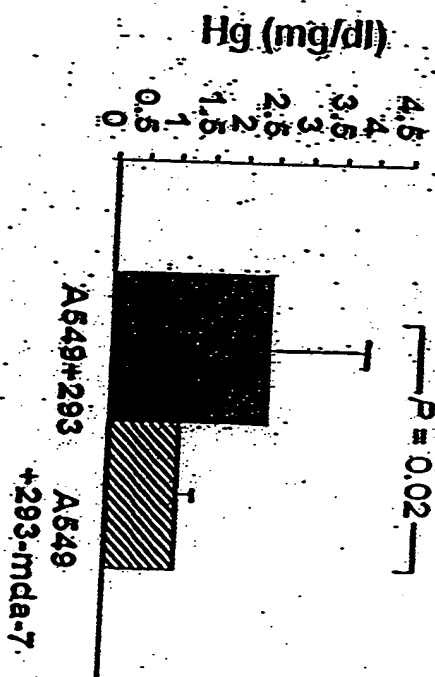


FIG. 6C

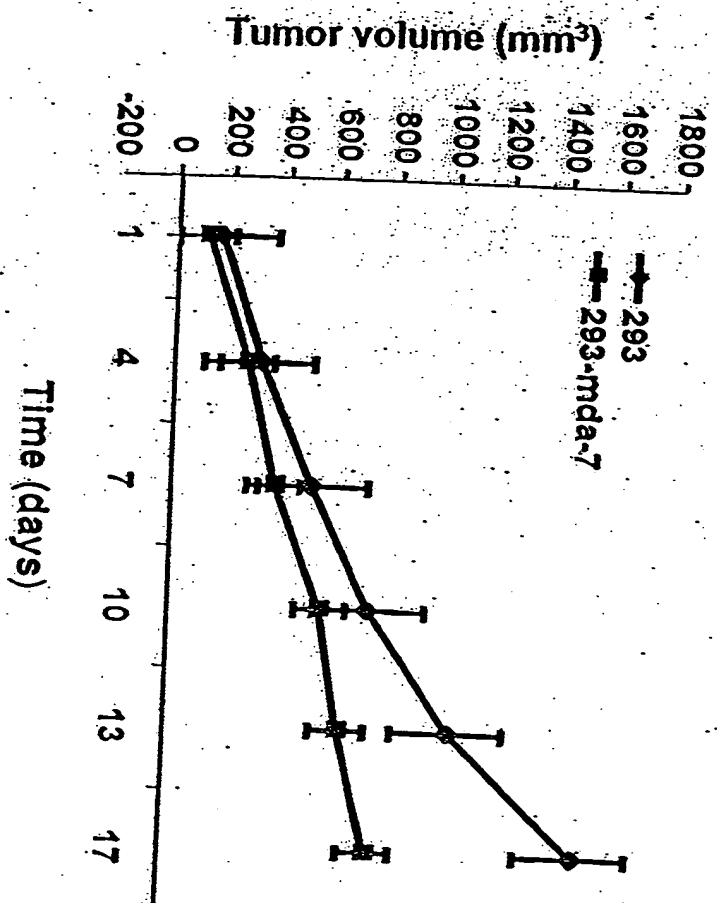


FIG. 6D

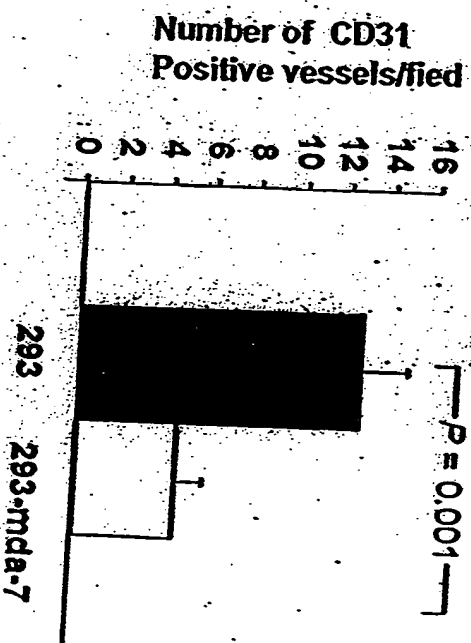


FIG. 6E

Study design

FIG. 7

Cohort #	# of patients	Viral dose (particles)	biopsy time (post inj.)
1	1	2×10^{10}	24 hrs
2	1	2×10^{11}	24 hrs
3	3	2×10^{12}	24 hrs
4	3	2×10^{12}	48 hrs
5	3	2×10^{12}	72/96 hrs
6	3	2×10^{12} (divided doses)	48 hrs
7	5	2×10^{12}	Core bx @30 days
8	5	2×10^{12} (2x/wk x 3 wks)	Core bx @ 30 days

FIG. 8

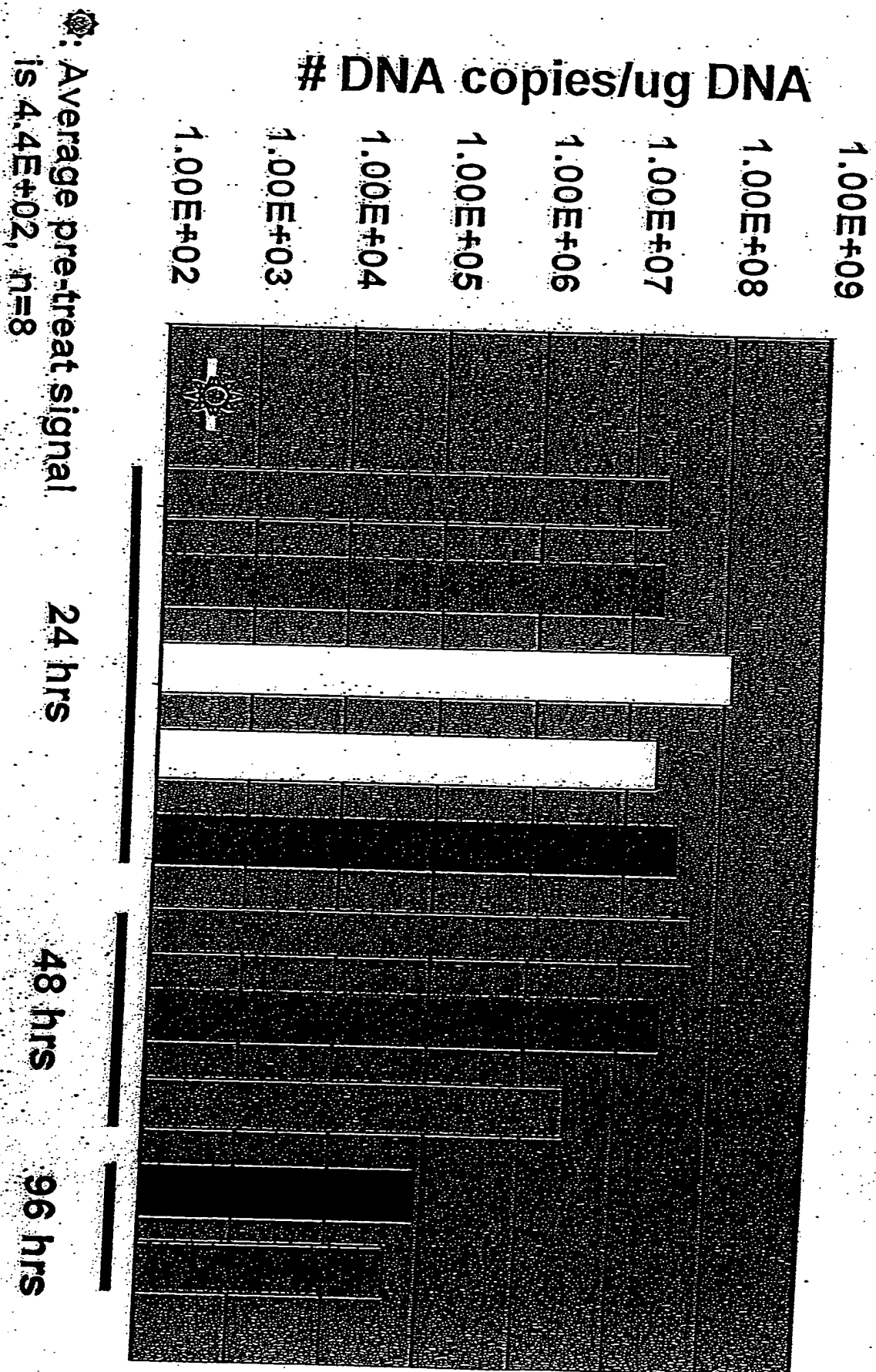


FIG. 9

(Pre-treat MDA-7 IHC - all negative)

<u>Pt</u>	<u>Time (hr)</u>	<u>MDA-7 ctr</u>	<u>MDA-7 periph</u>	<u>TUNEL ctr</u>	<u>TUNEL periph</u>
1	24	20%	0%	20%	0%
2	24	30%	5%	70%	10%
3	24	75%	40%	50%	30%
4	24	35%	5%	n.d.	n.d.
5	24	50%	25%	25%	17%
6	48	>60%	20%	40%	17%
7	48	60%	5%	70%	10%
8	48	20%	0%	5%	0%
9	96	50%	25%	80%	25%
10	96	90%	0%	35%	0%

MDA-7/TUNEL correlation is < 0.01

Kinetics of Serum Cytokine Response to INGN 241

FIG. 10

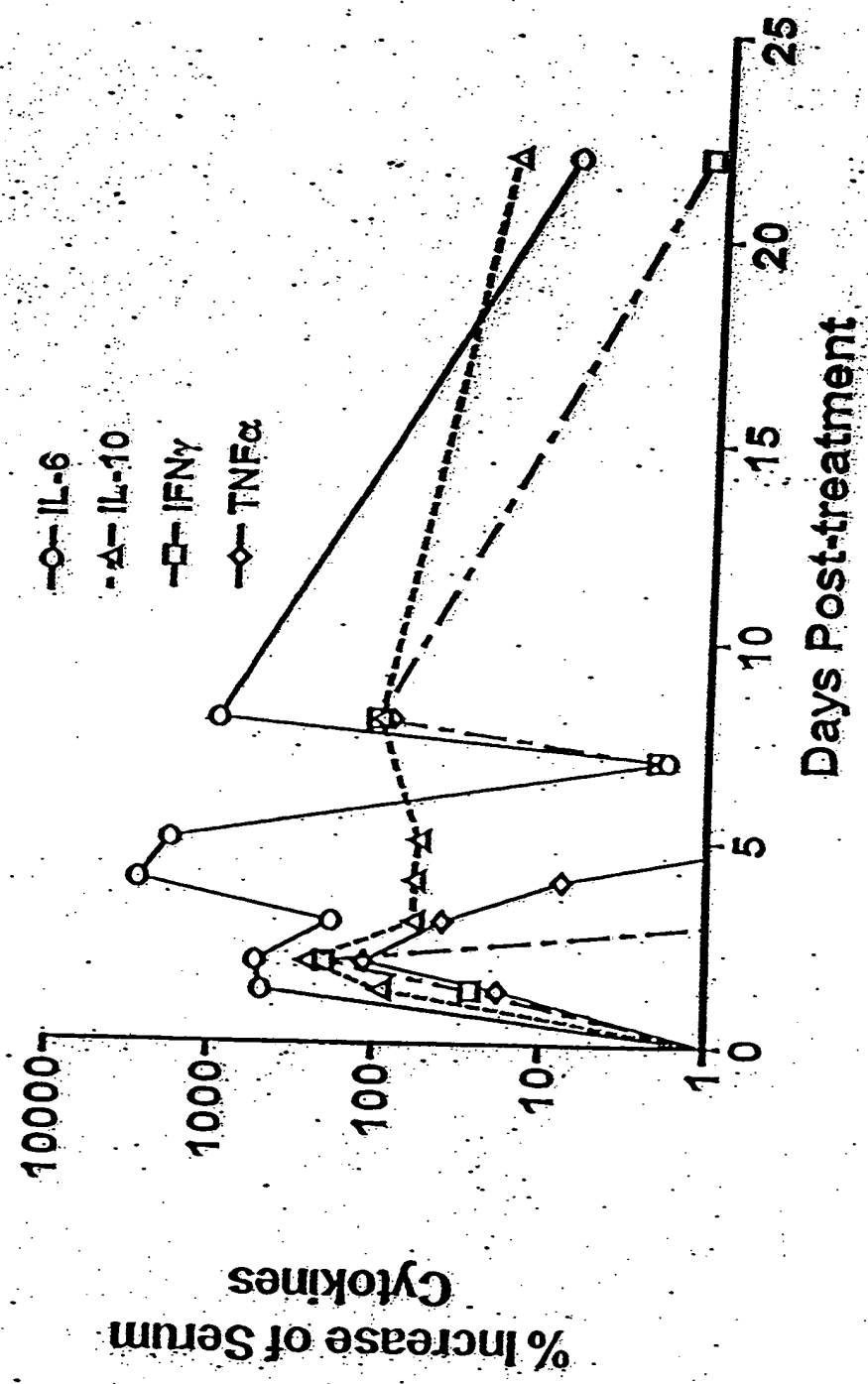


FIG. 11

Serum Cytokine Response to Intratumoral INGN 241 Treatment.

Cohort (dose)	No. pts tested	No. positive (mean % peak increase)			
		<u>IL-6</u>	<u>IL-10</u>	<u>IFNγ</u>	<u>TNFα</u> <u>GM-CSF</u>
1 (2×10^{10})	1	1 (298%)	1 (291%)	1 (>1,000%)	0 1 (150%)
2 (2×10^{11})	1	1 (143%)	1 (599%)	1 (281%)	1 (864%)
3 (2×10^{12})	3	1 (>1,000%)	1 (134%)	1 (317%)	2 (345%)
4 (2×10^{12})	3	3 (>1,000%)	3 (221%)	1 (173%)	2 (71%)
5 (2×10^{12})	3	3 (640%)	3 (400%)	1 (317%)	2 (156%)
7 (2×10^{12})	7	5 (604%)	6 (387%)	3 (860%)	3 (255%)
Total	18	14	15	8	10
					3

FIG. 12

Level of Increased CD8+ T cell Frequency in Pts who Received Intratumoral INGN 241.

<u>Cohort</u> (dose)	<u>No. pts</u> <u>tested</u>	<u>No. with</u> <u>increased</u> <u>CD8+ T cells</u>	<u>Mean % CD3+CD8+ T cells¹</u>		
			<u>Pre-</u> <u>treatment</u> 29 %	<u>Post-</u> <u>treatment @</u> 27%	<u>Day</u> <u>Post-treat.</u>
1 (2x10 ¹⁰)	1	0			
2 (2x10 ¹¹)	1	1	32 %	44%	Day 15
3 (2x10 ¹²)	3	3	33%	59%	Day 15
4 (2x10 ¹²)	3	1	35%	44%	Day 30
5 (2x10 ¹²)	3	1	22%	29%	Day 15
7 (2x10 ¹²)	7	2	30%	40%	Days 15-30
Total	18	8	31%	44%	Day 15

FIG. 13

Increase in Peripheral Blood CD8+ T Cells Following intratumoral INGN 241 Injection

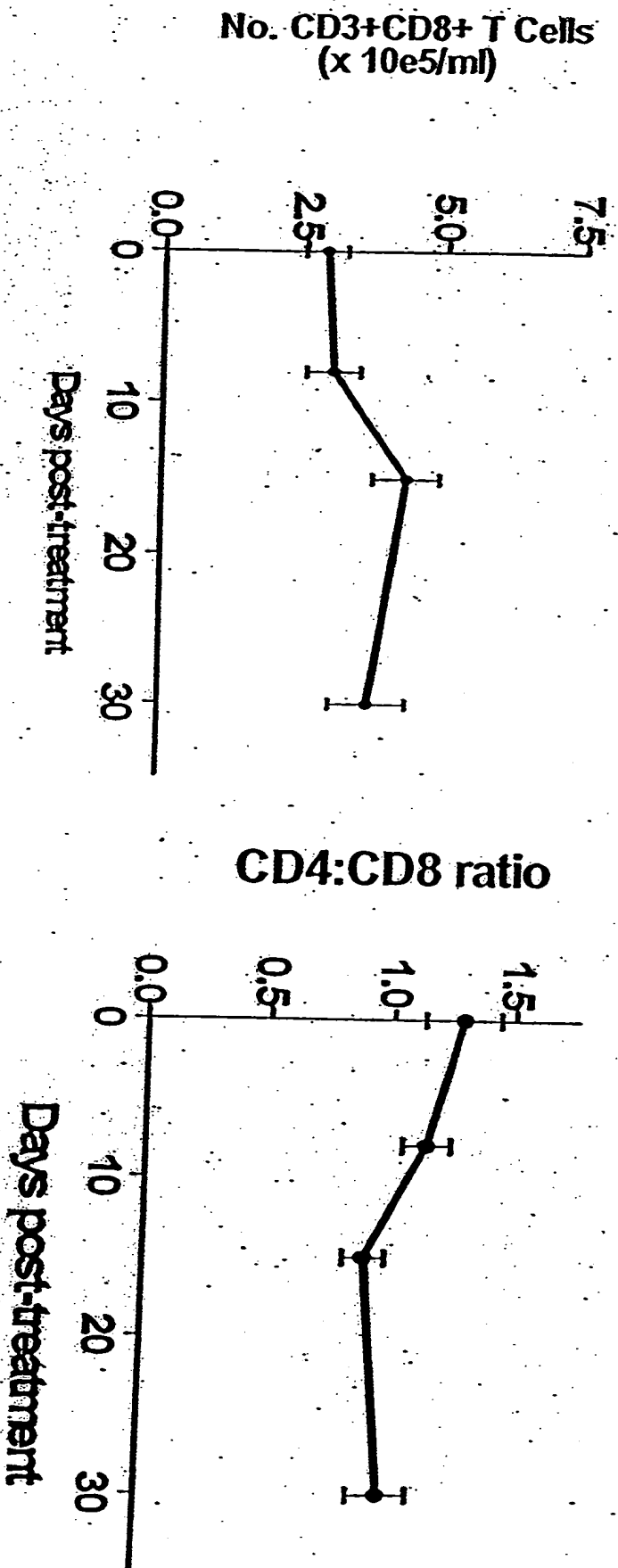


FIG. 14

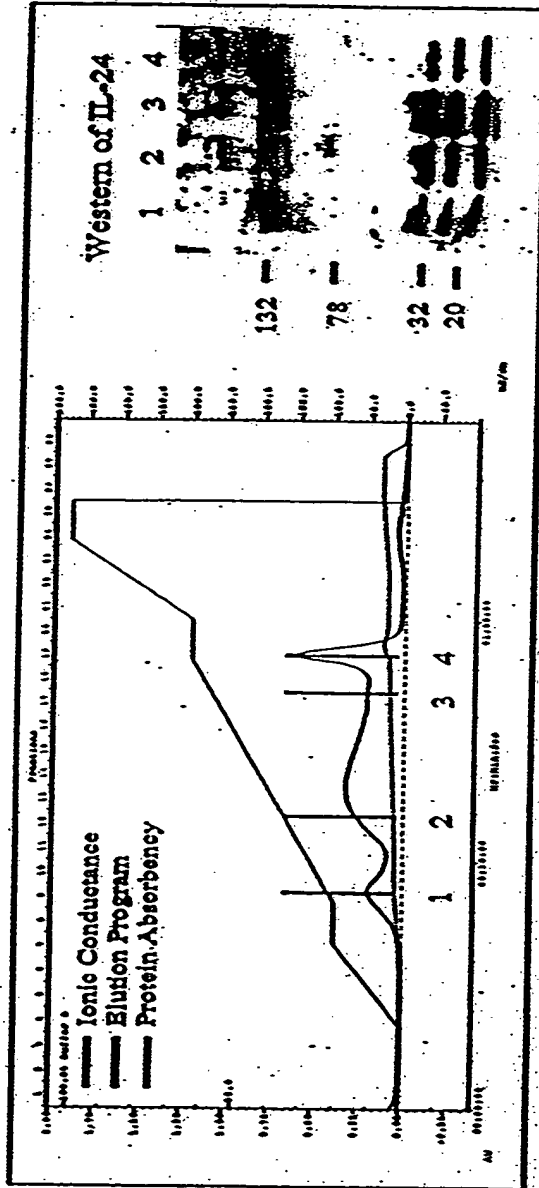
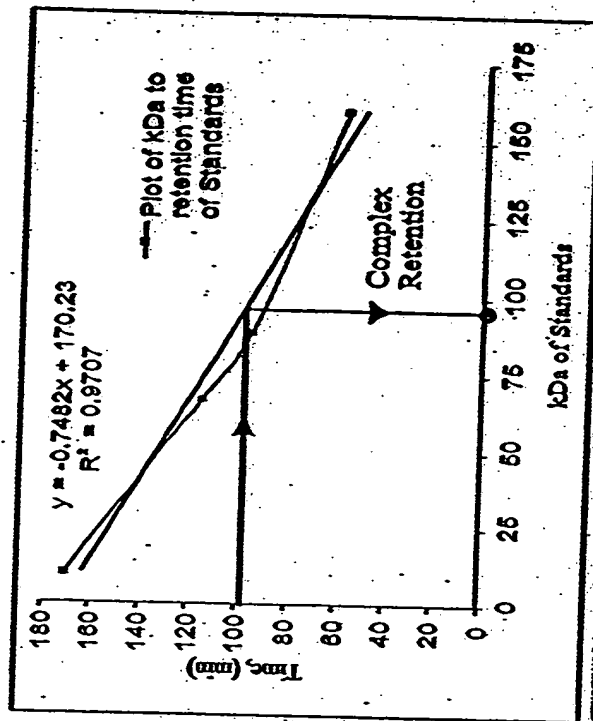


FIG. 15



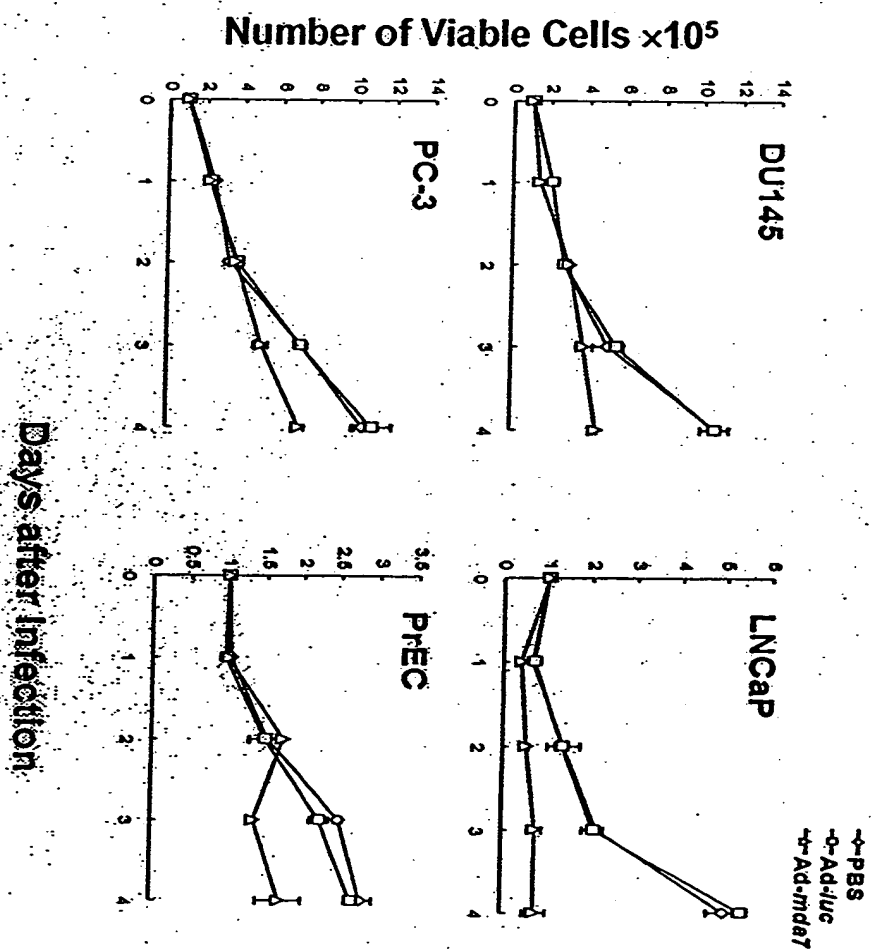


FIG. 16

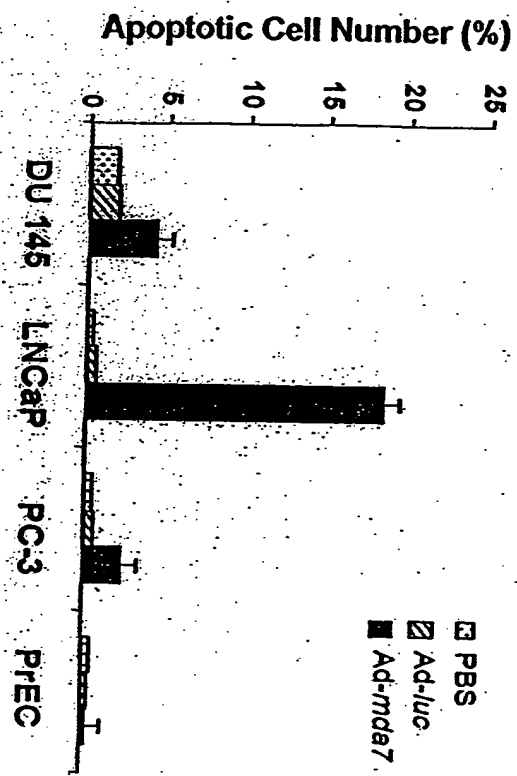
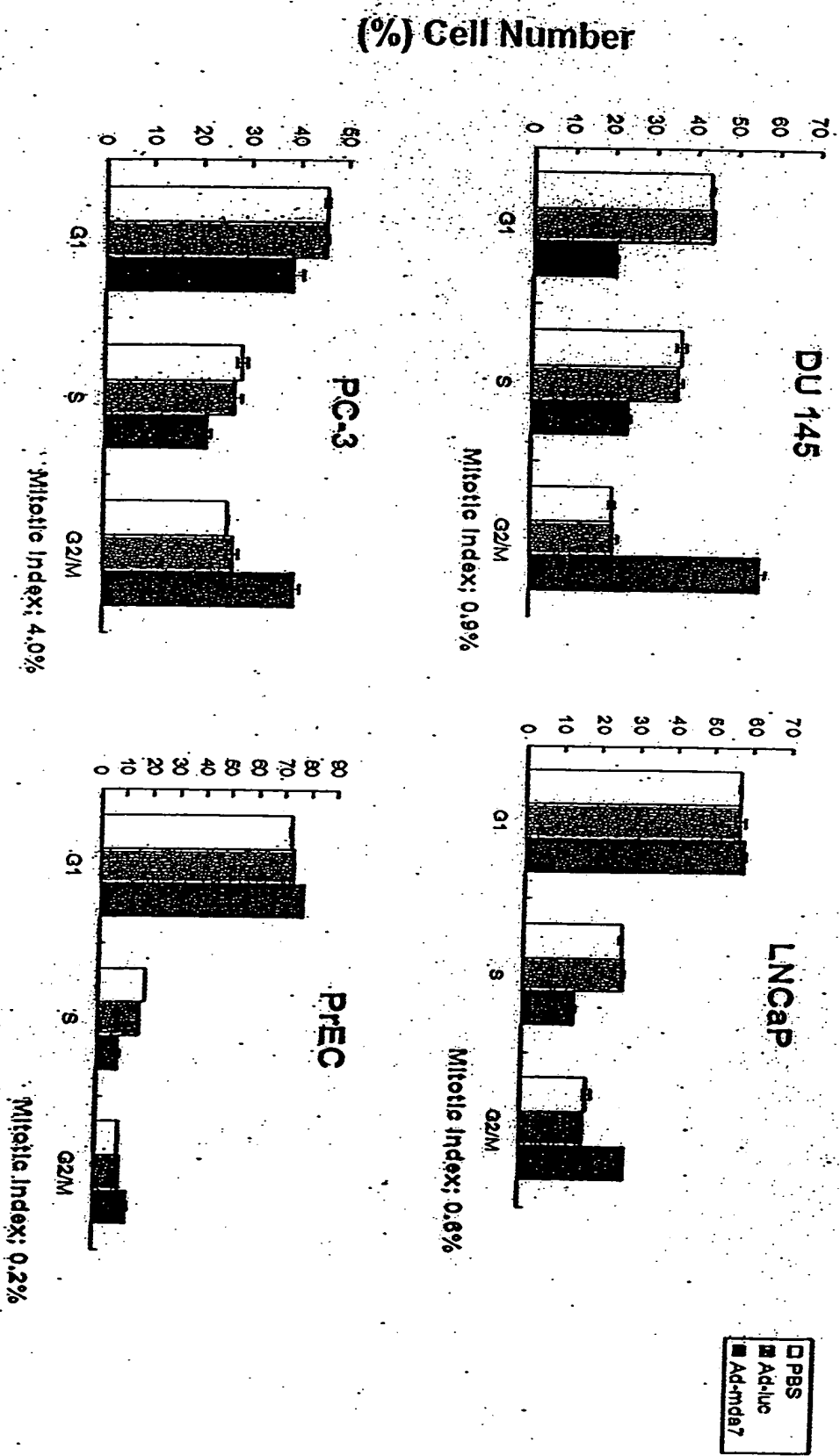


FIG. 17



Cell Cycle Phase

FIG. 18

FIG. 19A

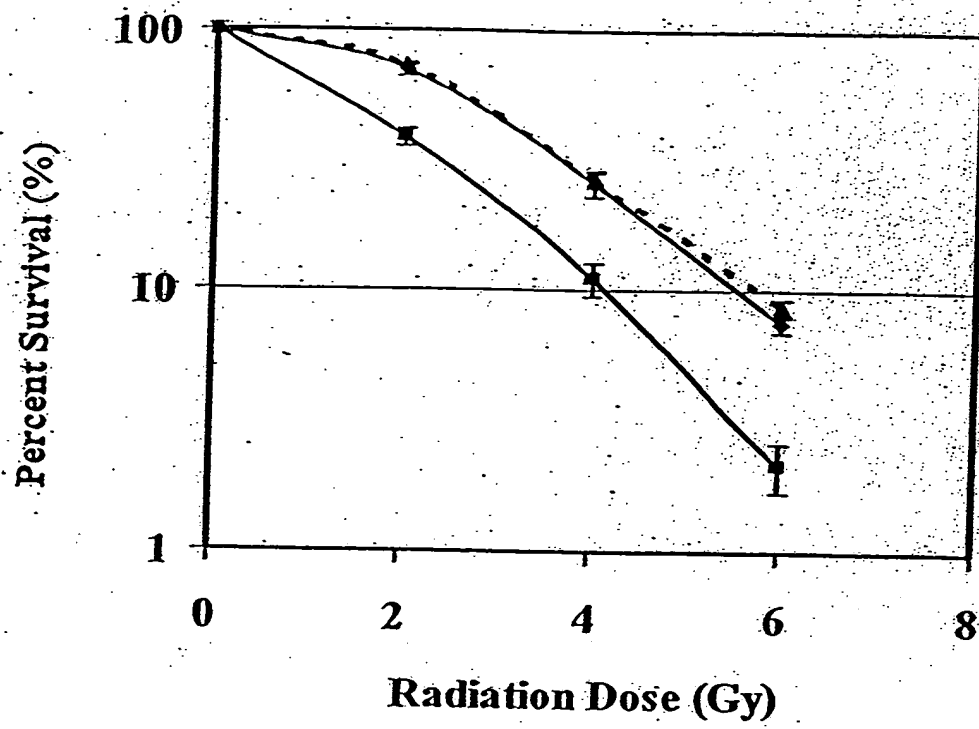


FIG. 19B

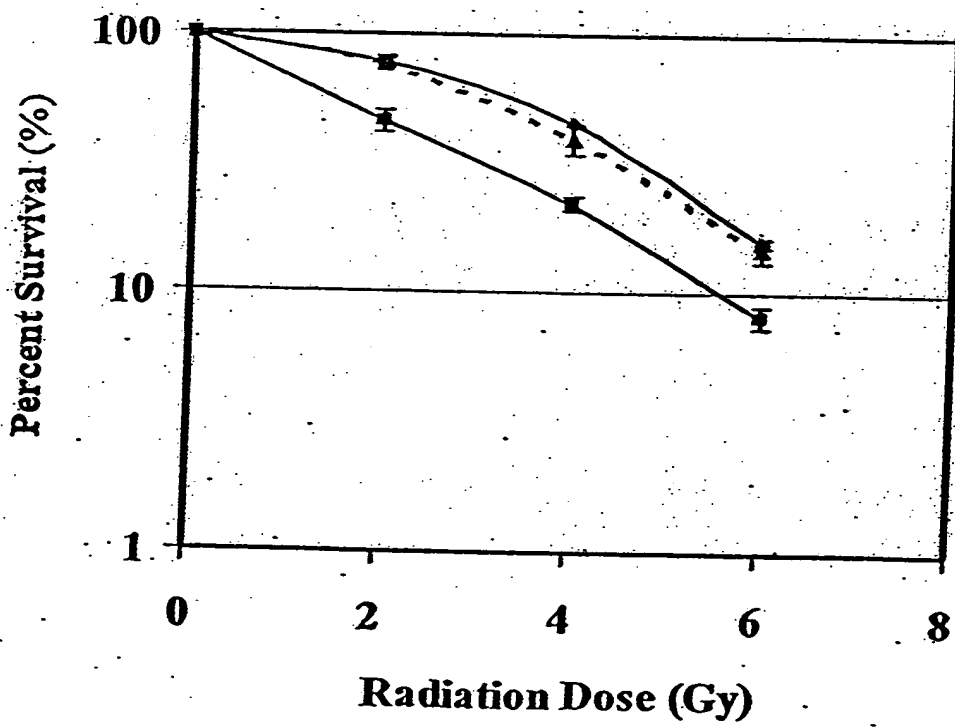


FIG. 19C

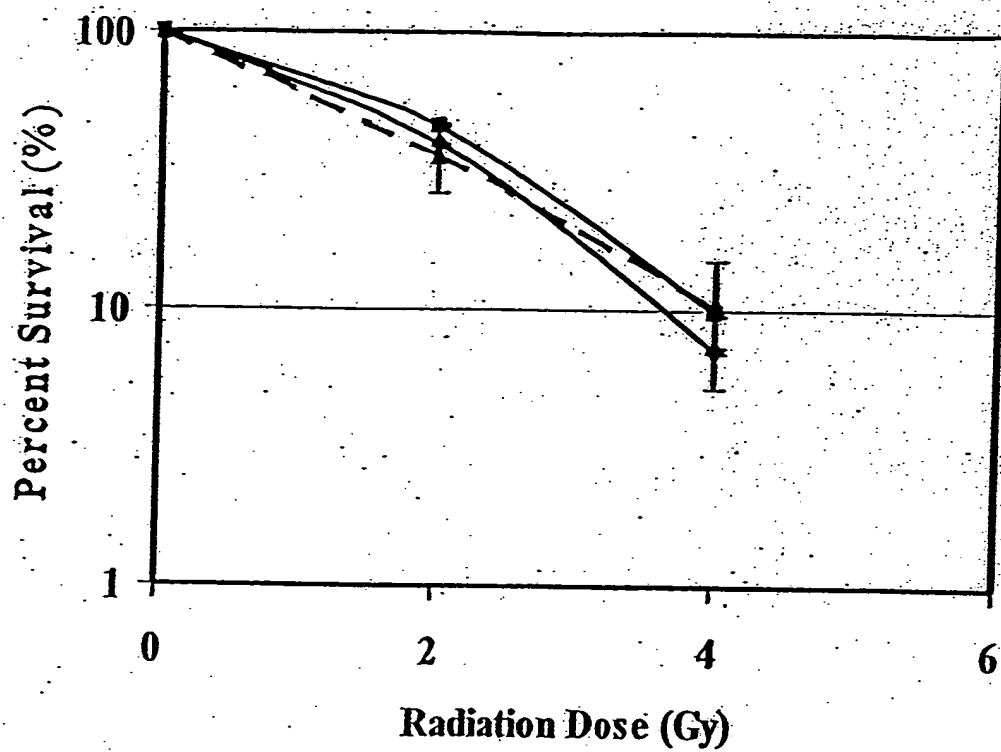


FIG. 19D

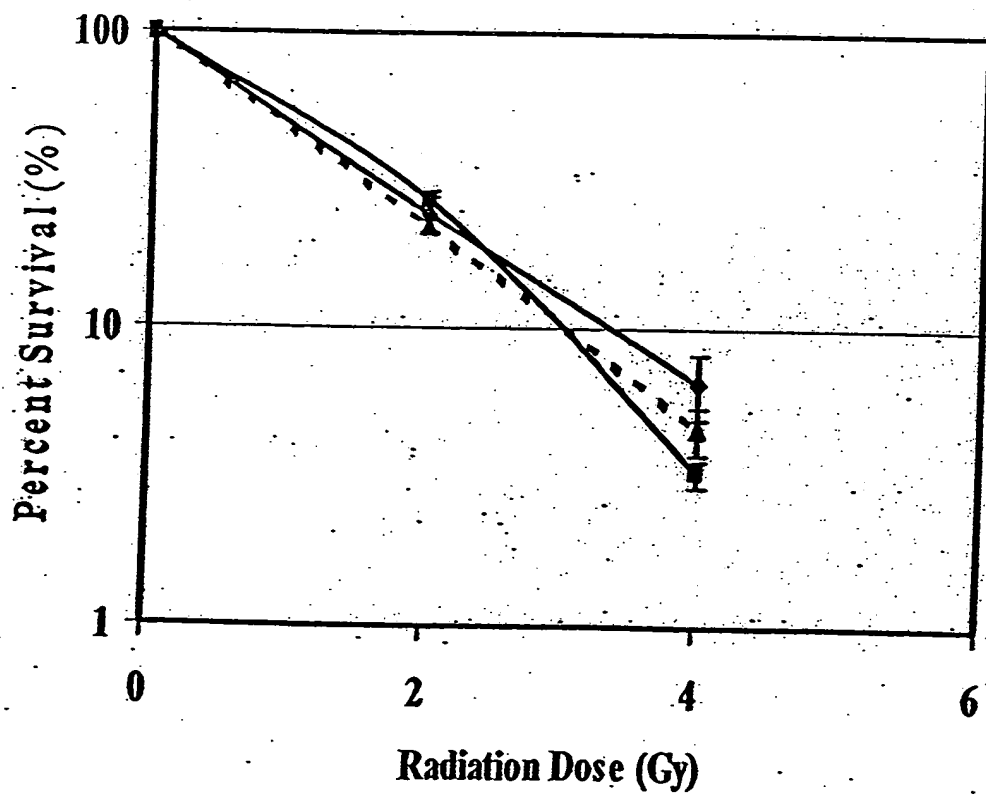


FIG. 20A

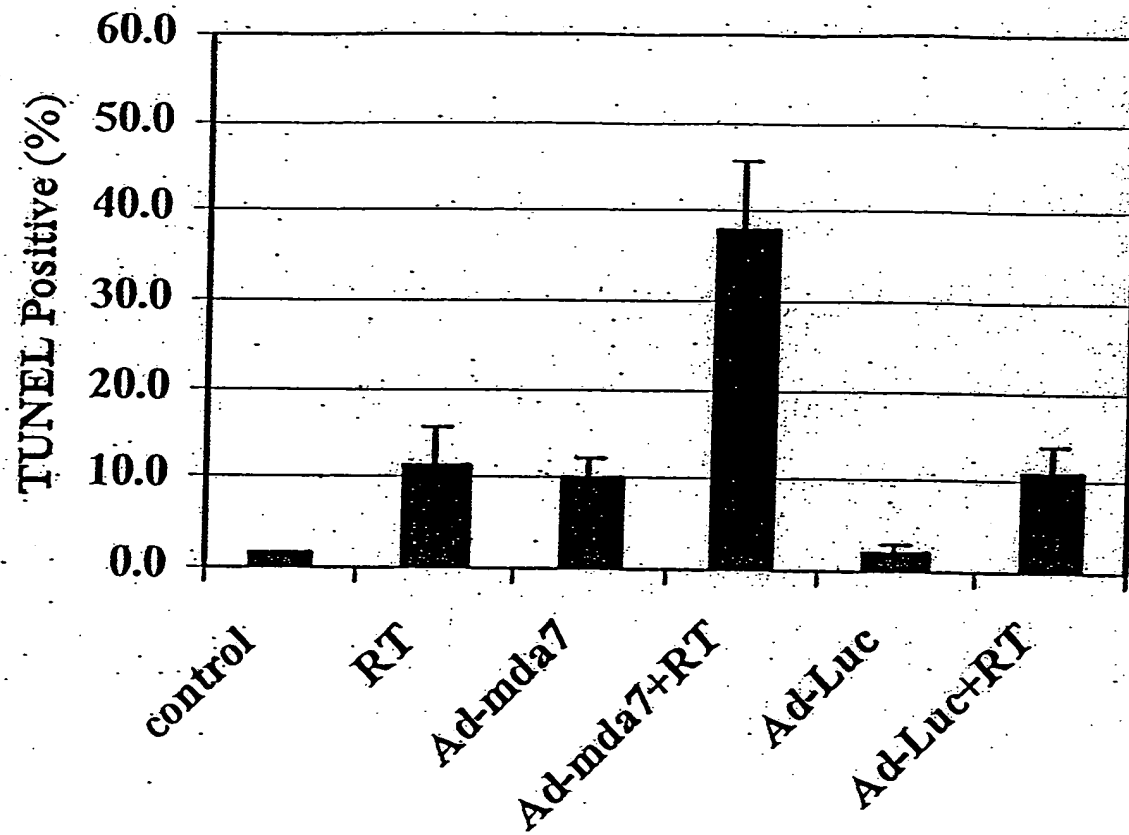


FIG. 20B

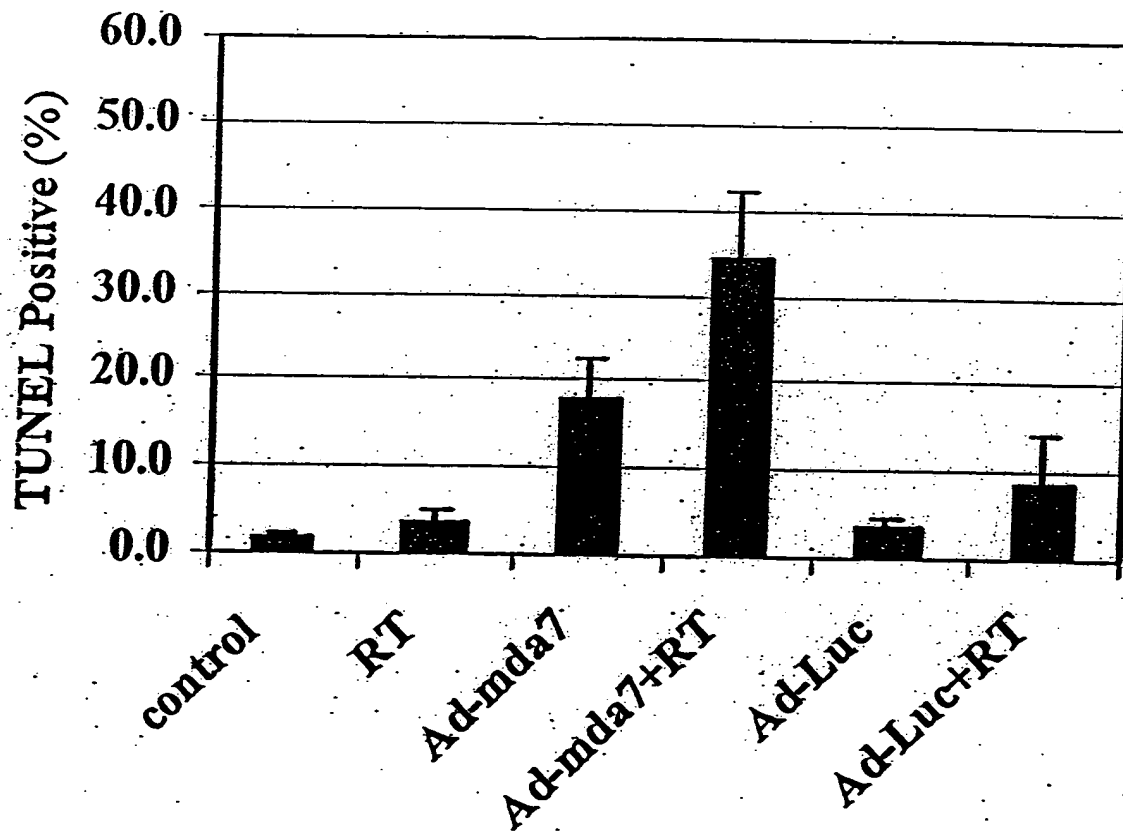


FIG. 20C

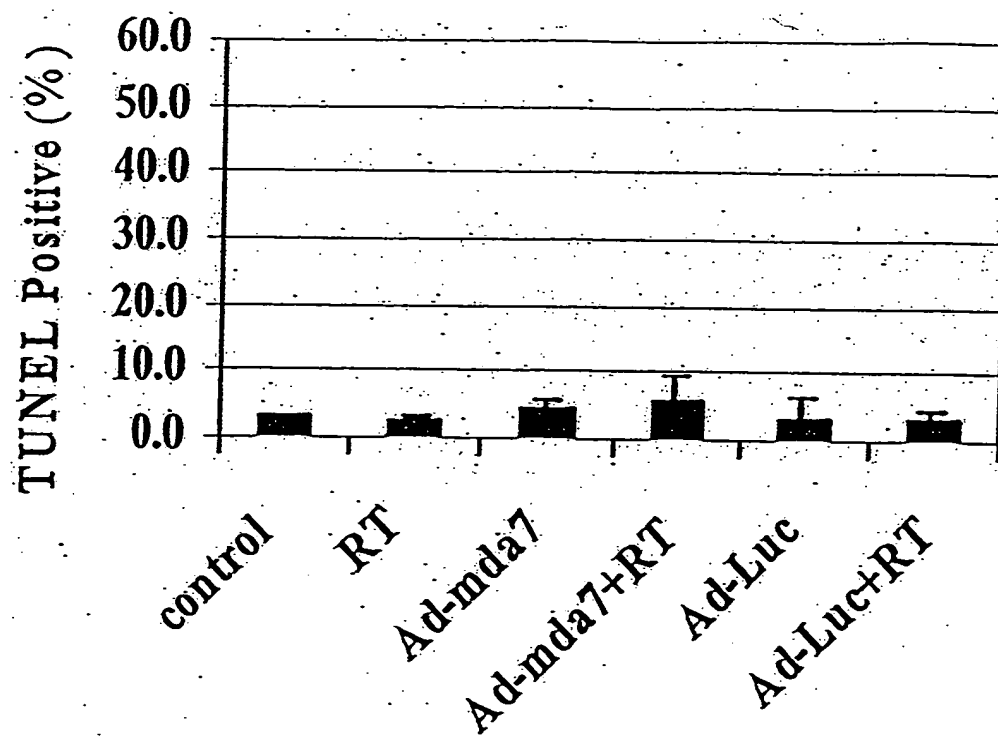
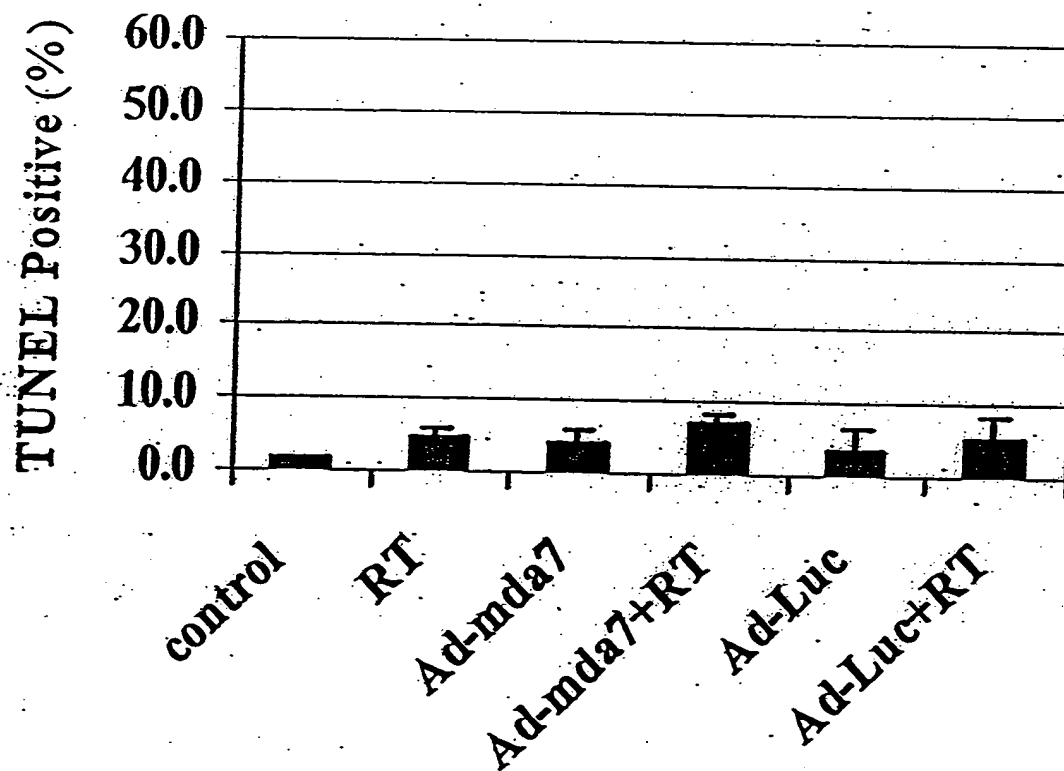


FIG. 20D



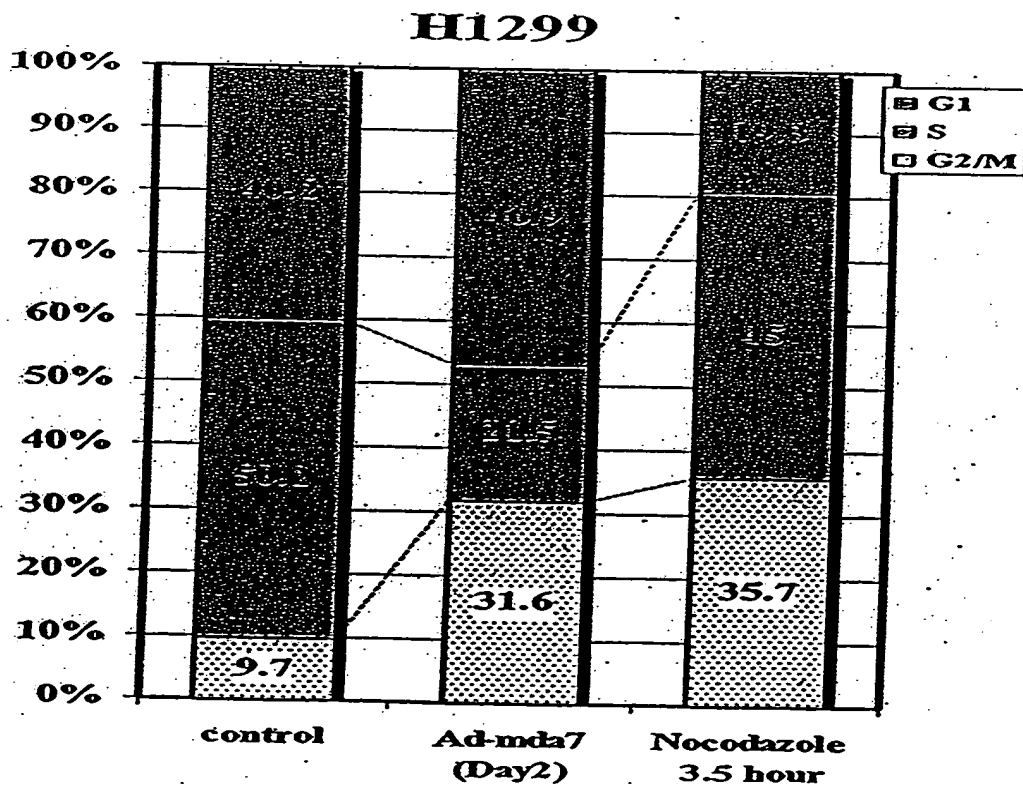
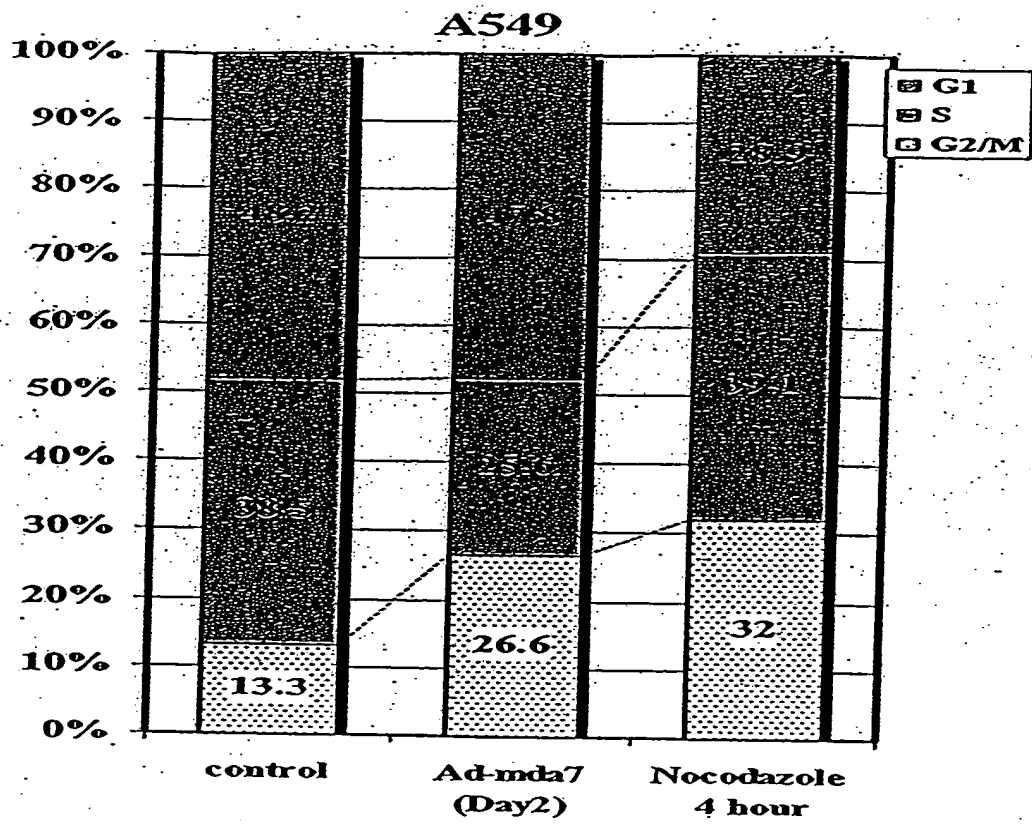


FIG. 21

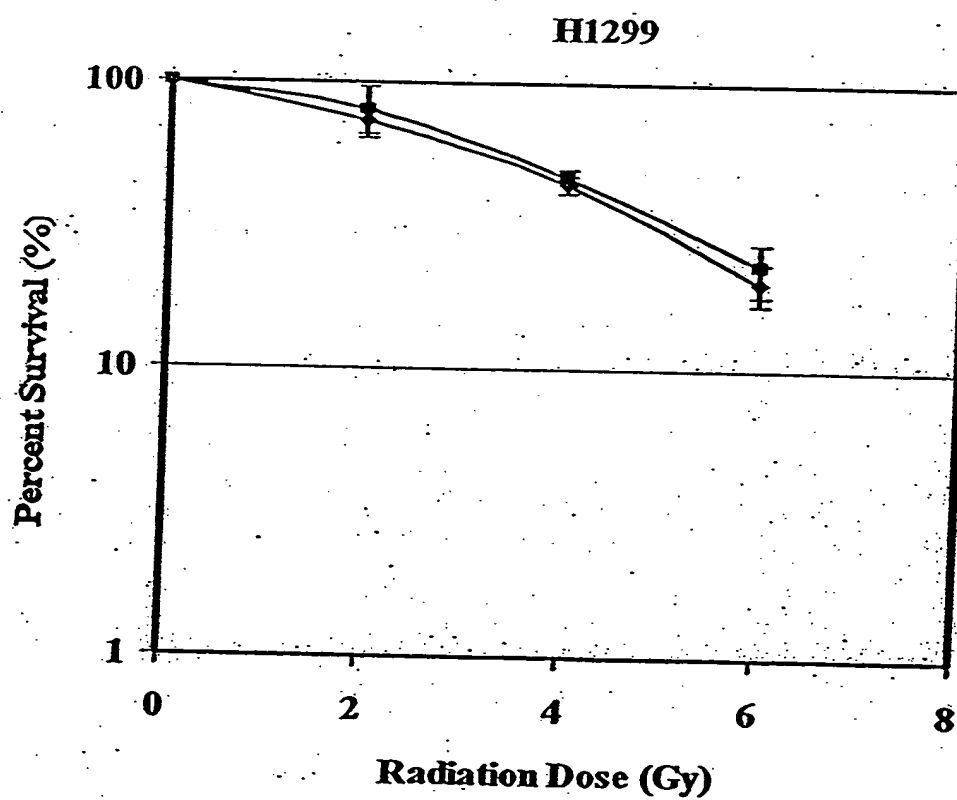
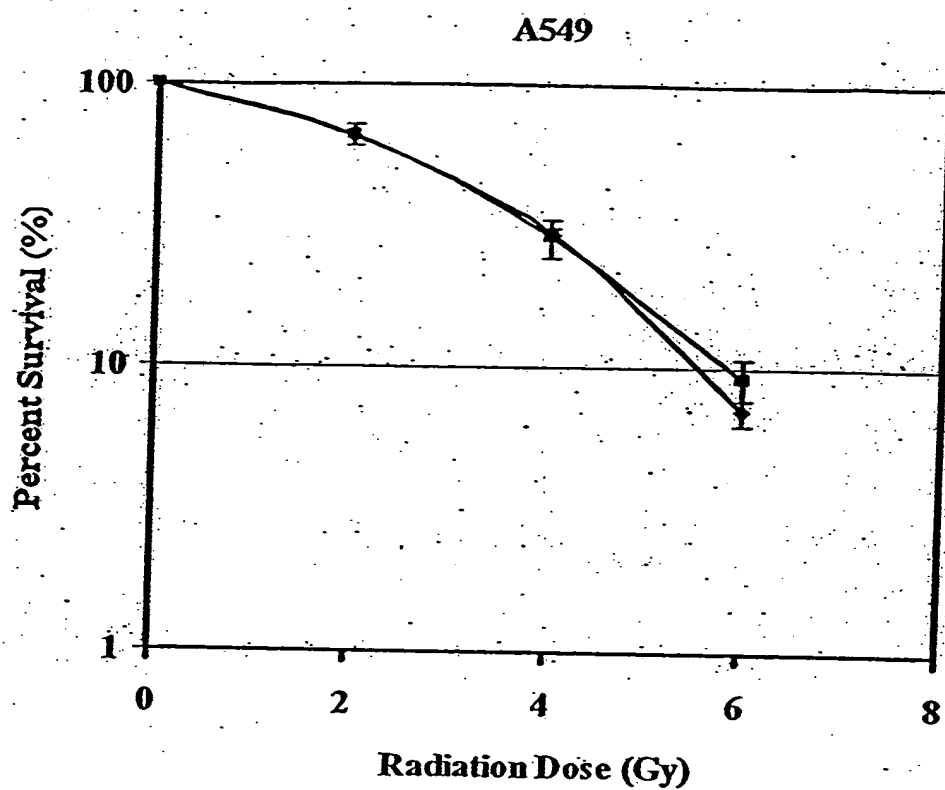
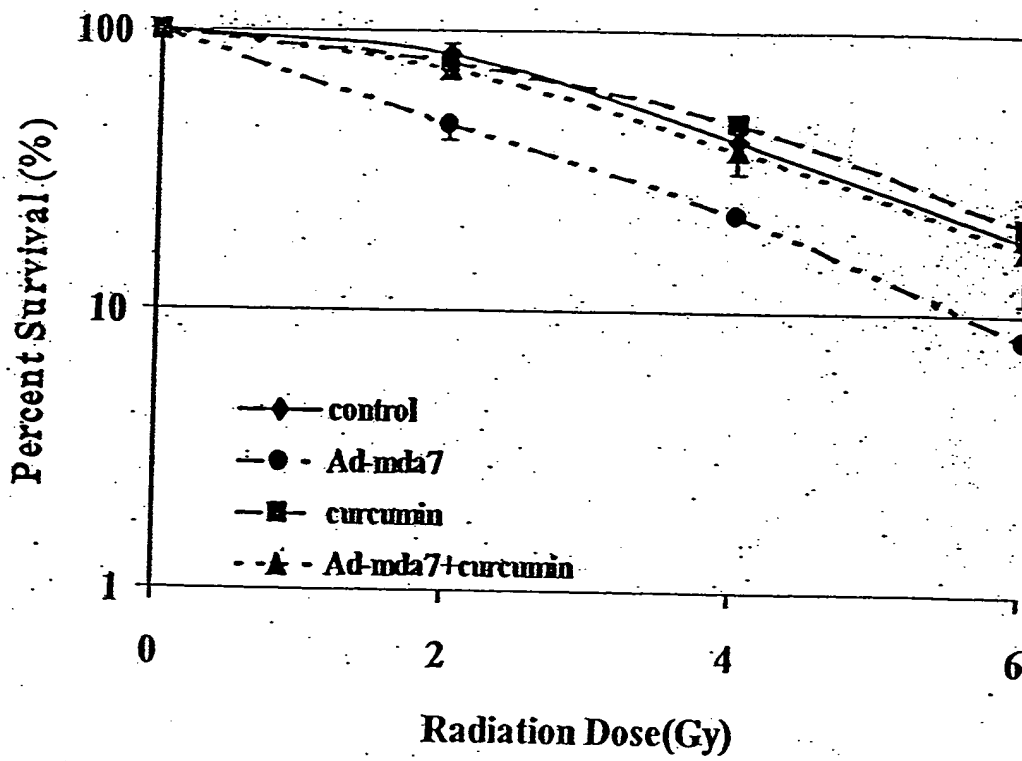


FIG. 22

H1299



A549

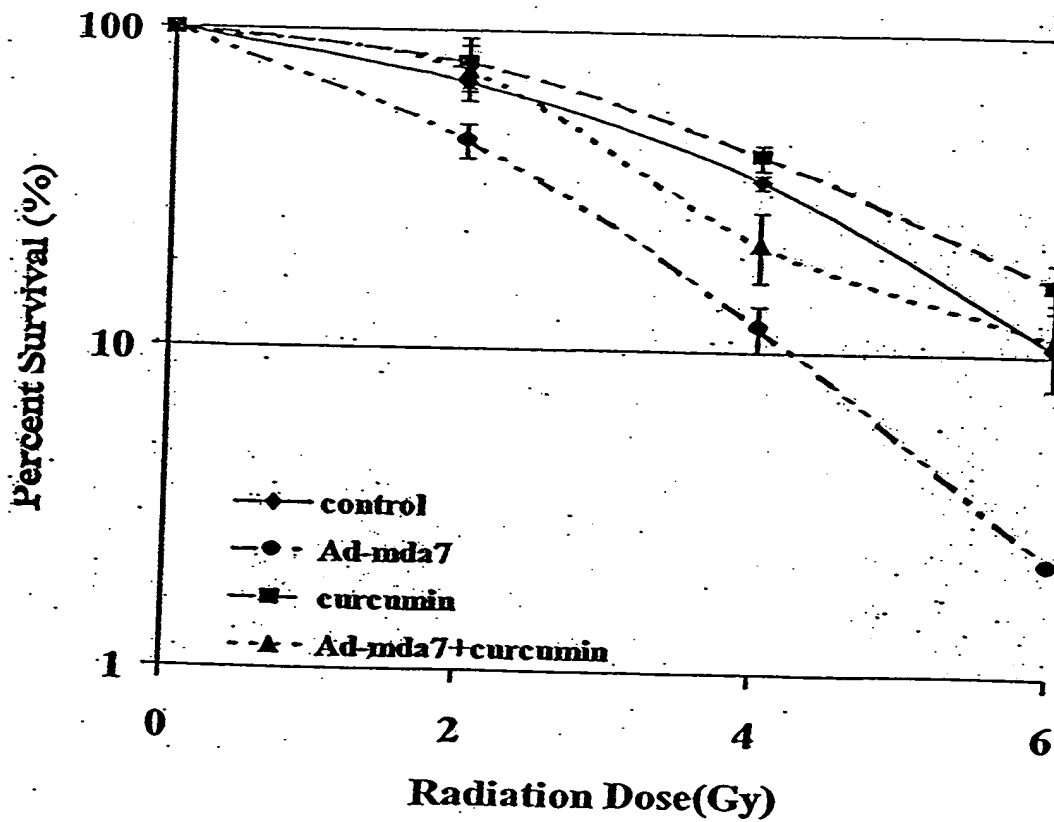


FIG. 23

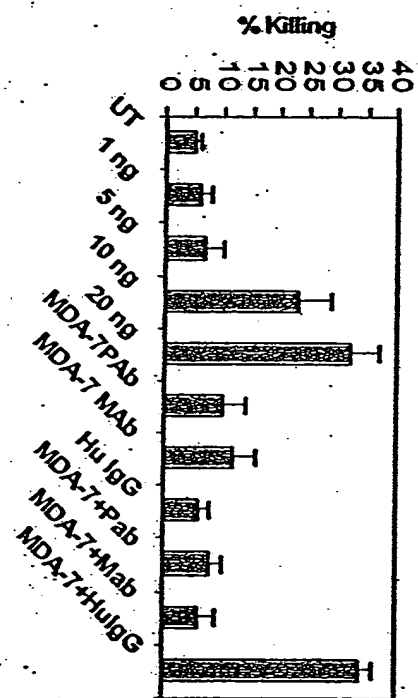
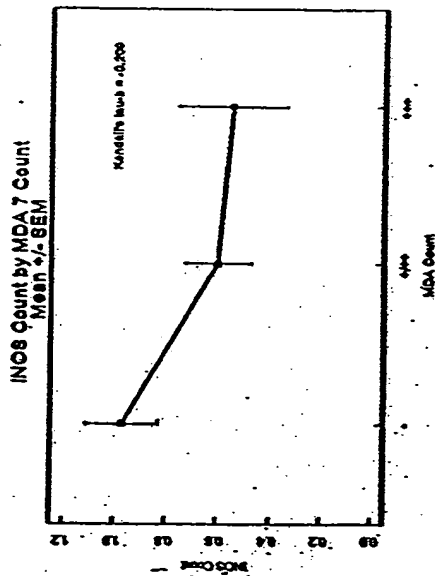


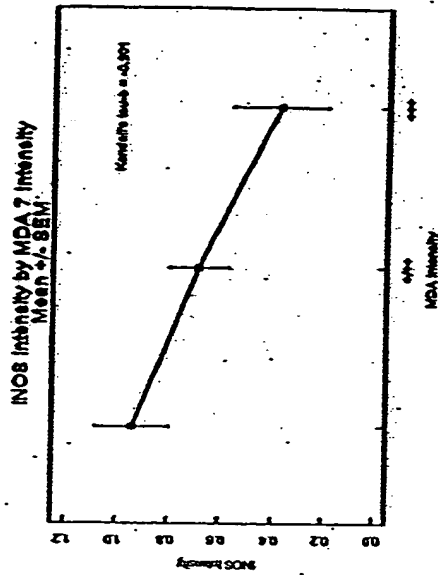
FIG. 24

A



MDA-7 count	Average INOS count	SE	N
-	.97	.13	35
+/+	.50	.12	35
+++	.54	.21	11

B



MDA-7 count	Average INOS count	SE	N
-	1.21	.16	32
+/+	.80	.14	41
+++	.80	.27	6

FIG. 25

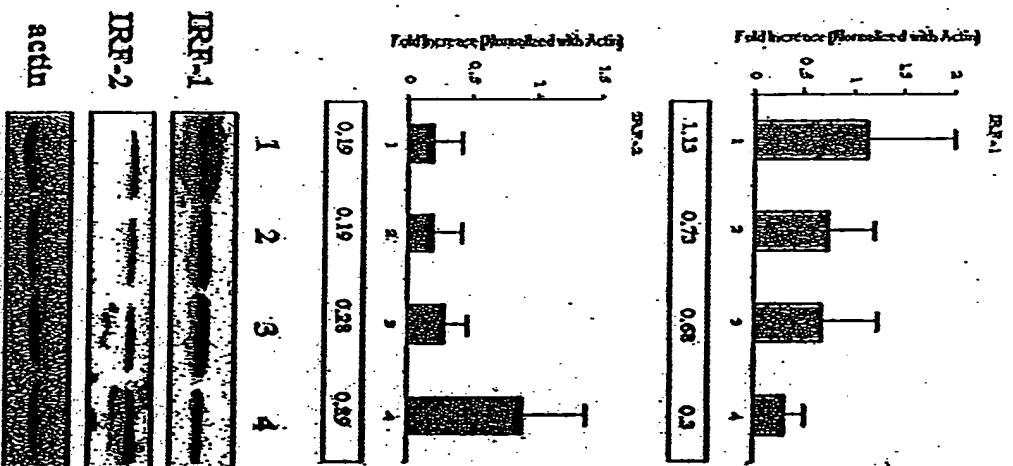


FIG. 26

FIG. 27

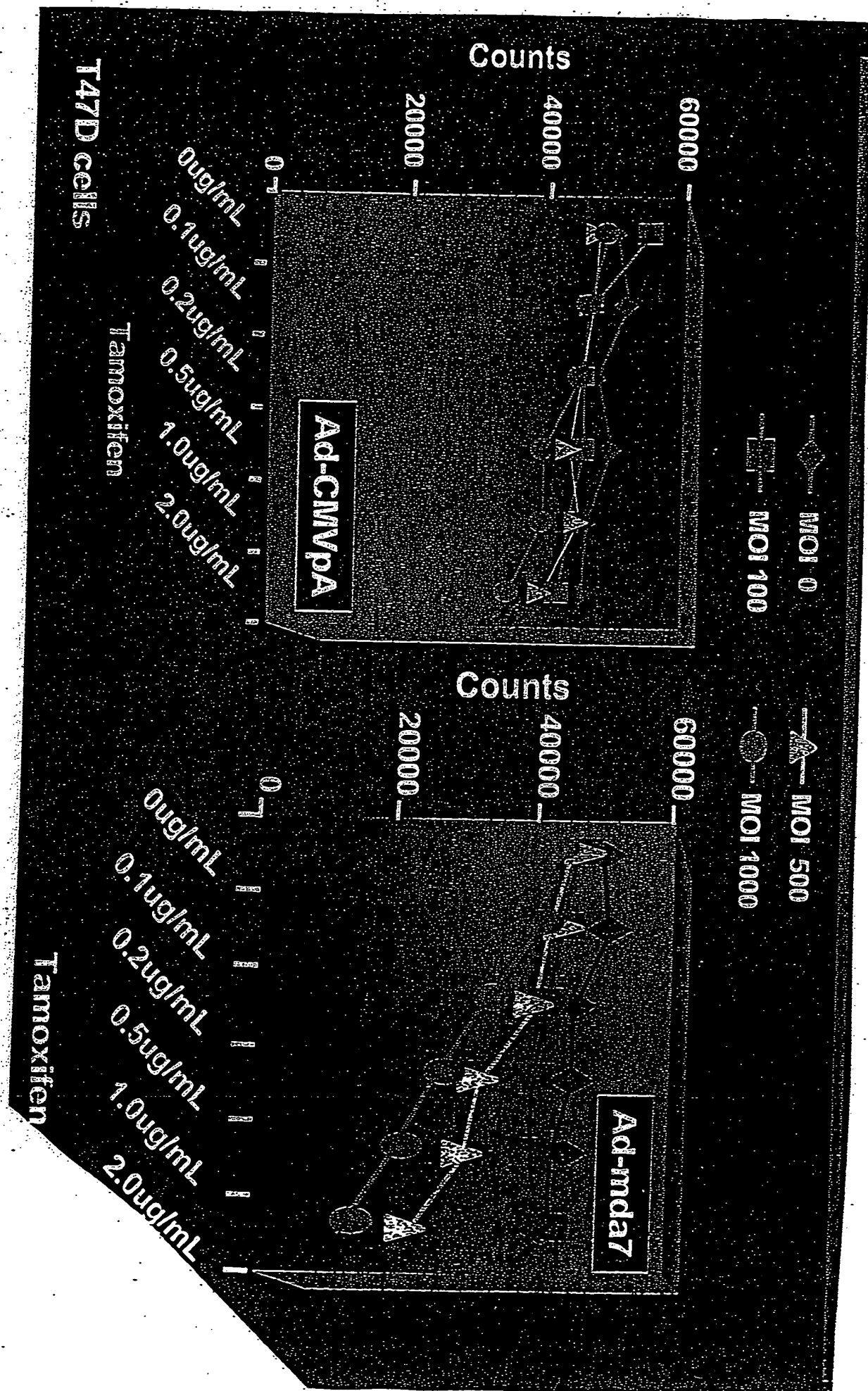


FIG. 28

<u>IL-6</u>	<u>IFN-γ</u>	<u>IL-10</u>	<u>GM-CSF</u>	<u>s.Fas</u>	<u>IL-1b</u>	<u>TNF-a</u>	<u>pSTAT3</u>
-------------	--------------------------------	--------------	---------------	--------------	--------------	--------------	---------------

Ad-	++	++	decrease	+/-	++	-	++
mda7							

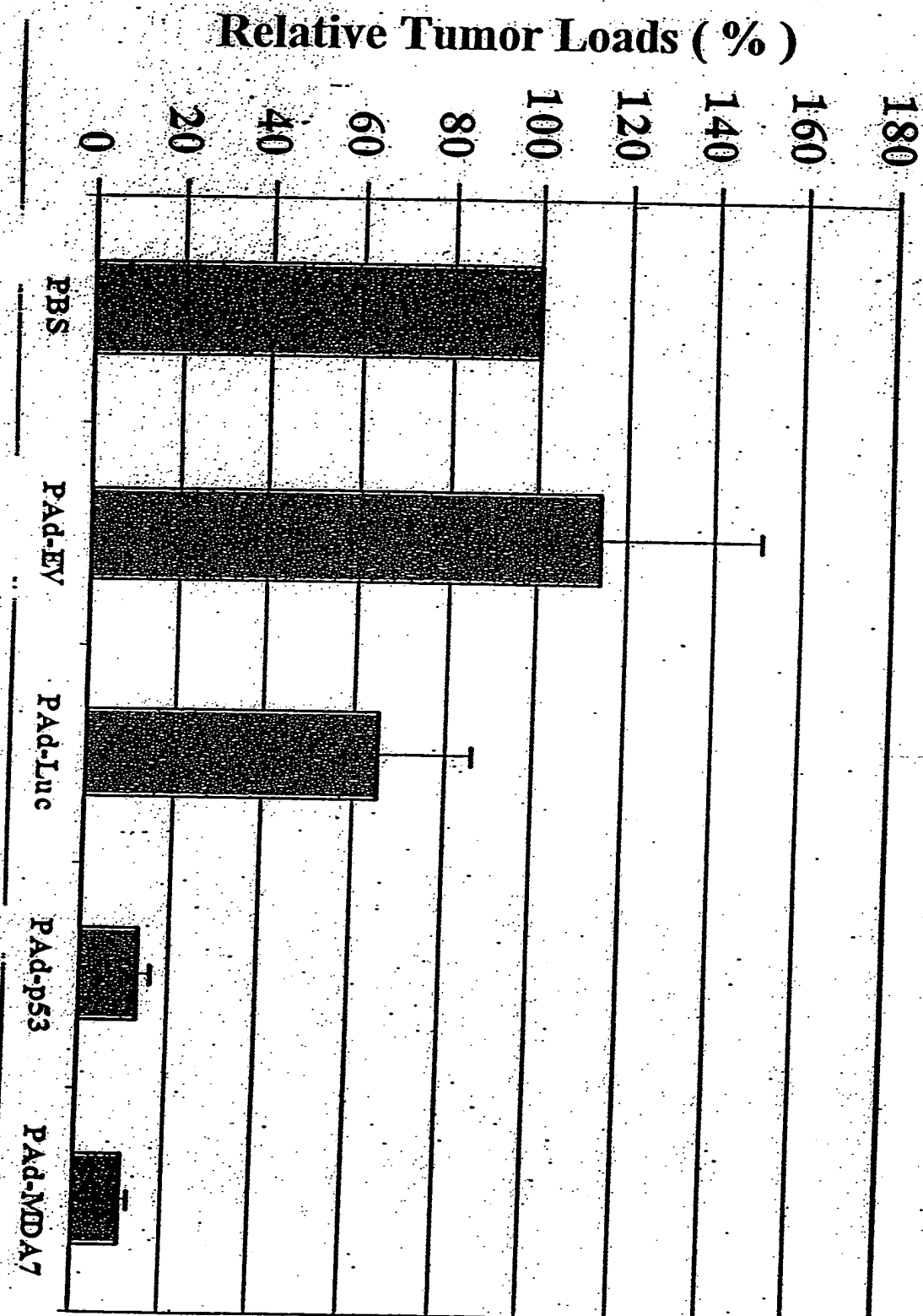
MDA-7	+	+++	decrease	n.d.	n.d.	n.d.	++
-------	---	-----	----------	------	------	------	----

++>+++ : increased cytokine secretion compared to Ad-luc control
 - : no change; n.d.: not done.

Cytokine levels were evaluated using ELISA from cultured cell supernatants taken 24-72 hr post treatment.
 pSTAT3 results were analyzed 4hr after addition of MDA-7 protein and 24 hr after Ad-mda7 treatment using IHC.

FIG. 29

Effect of Ad-mda7 on A549 Lung Metastasis



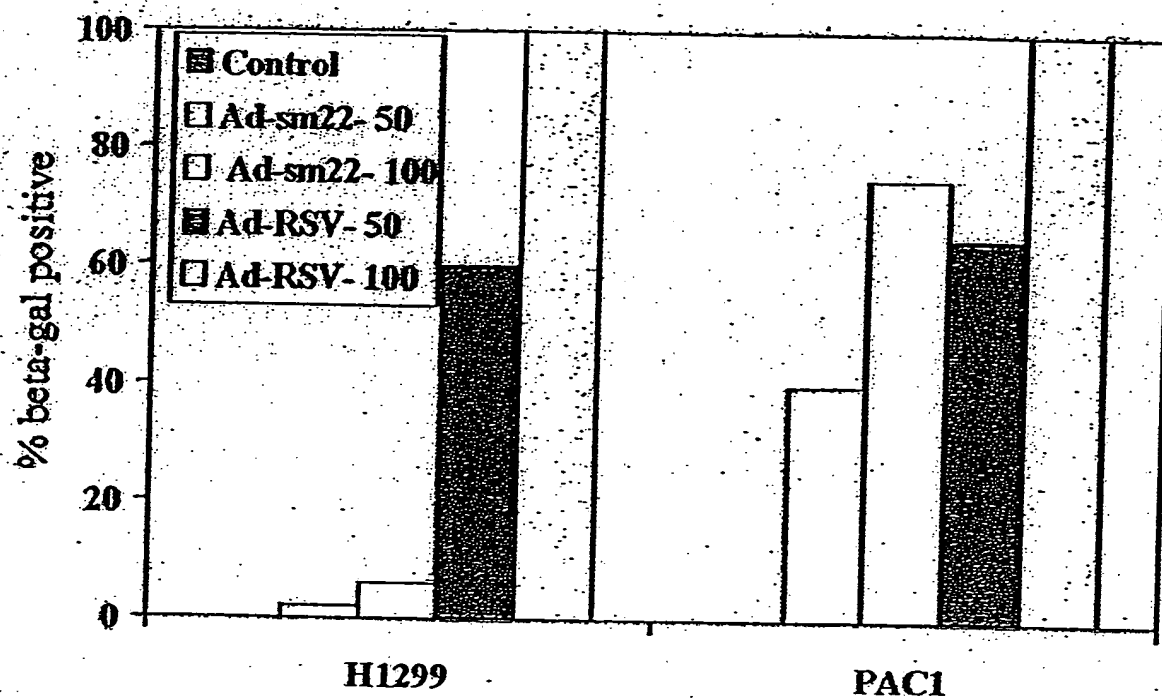


FIG. 30

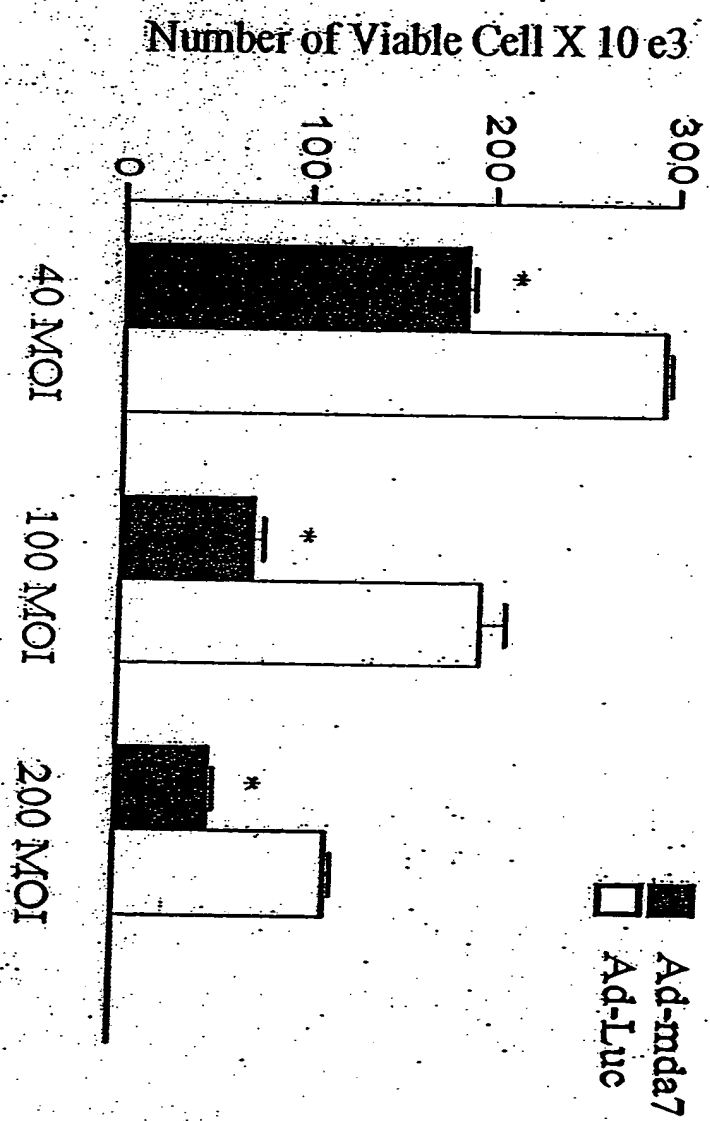


FIG. 31

A

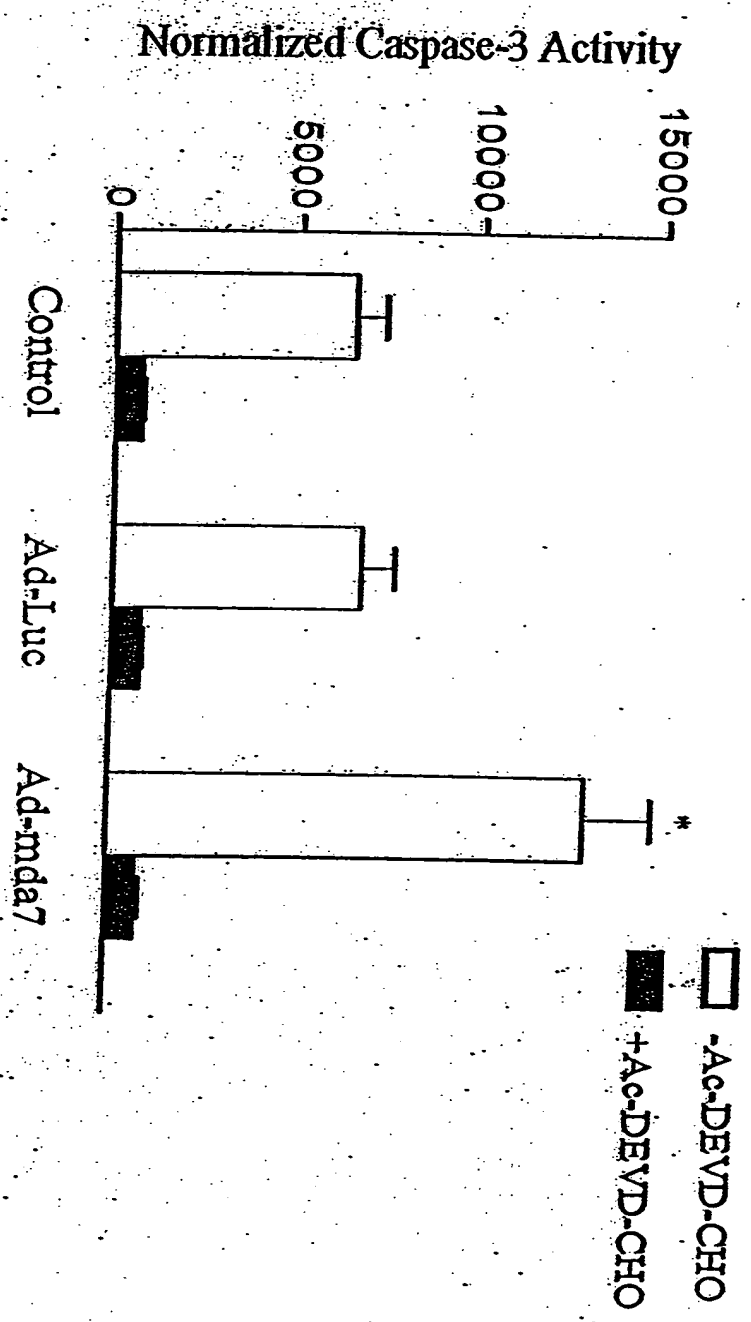


FIG. 32A

B

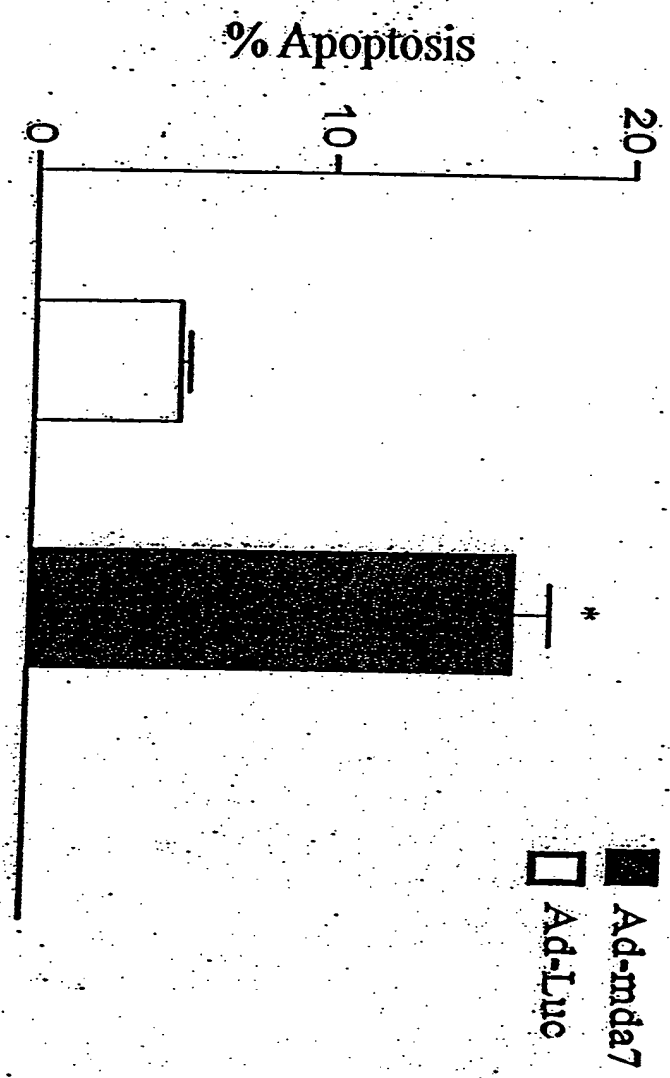


FIG. 32B

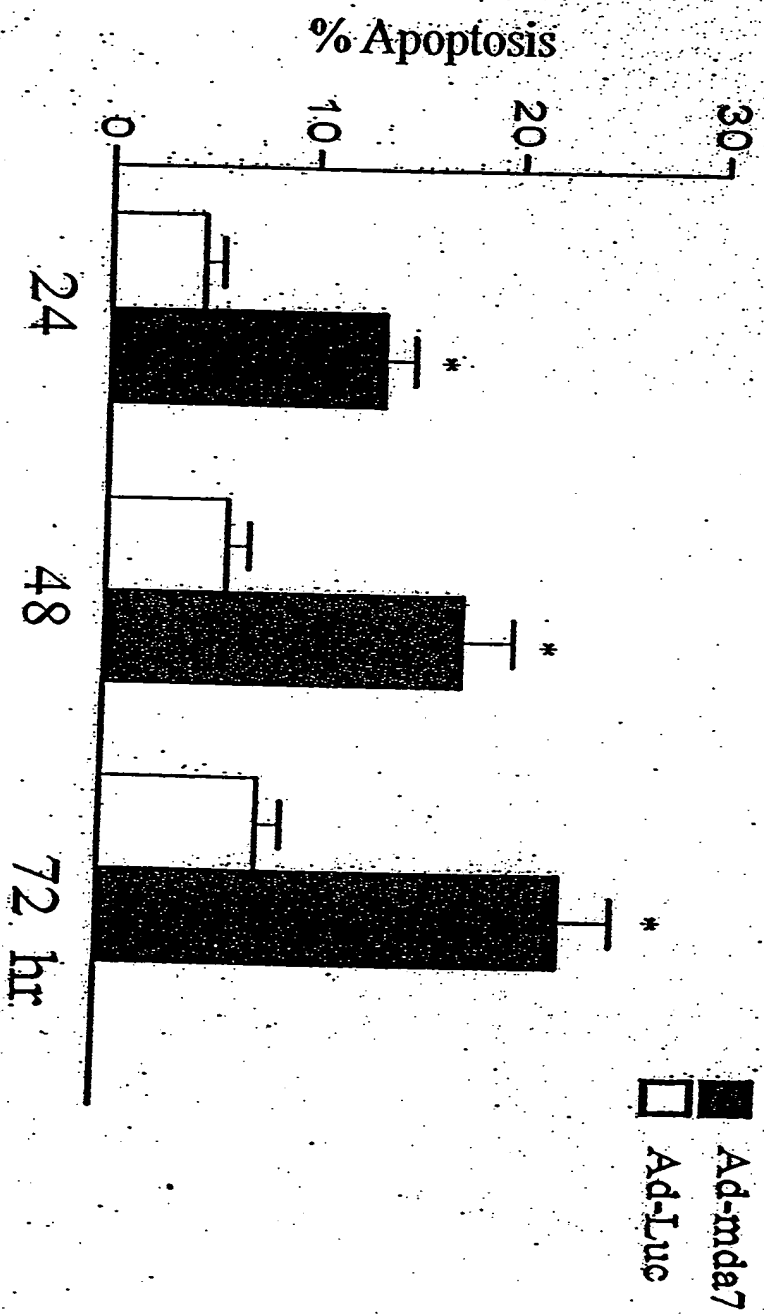


FIG. 32C

FIG. 33



FIG. 34

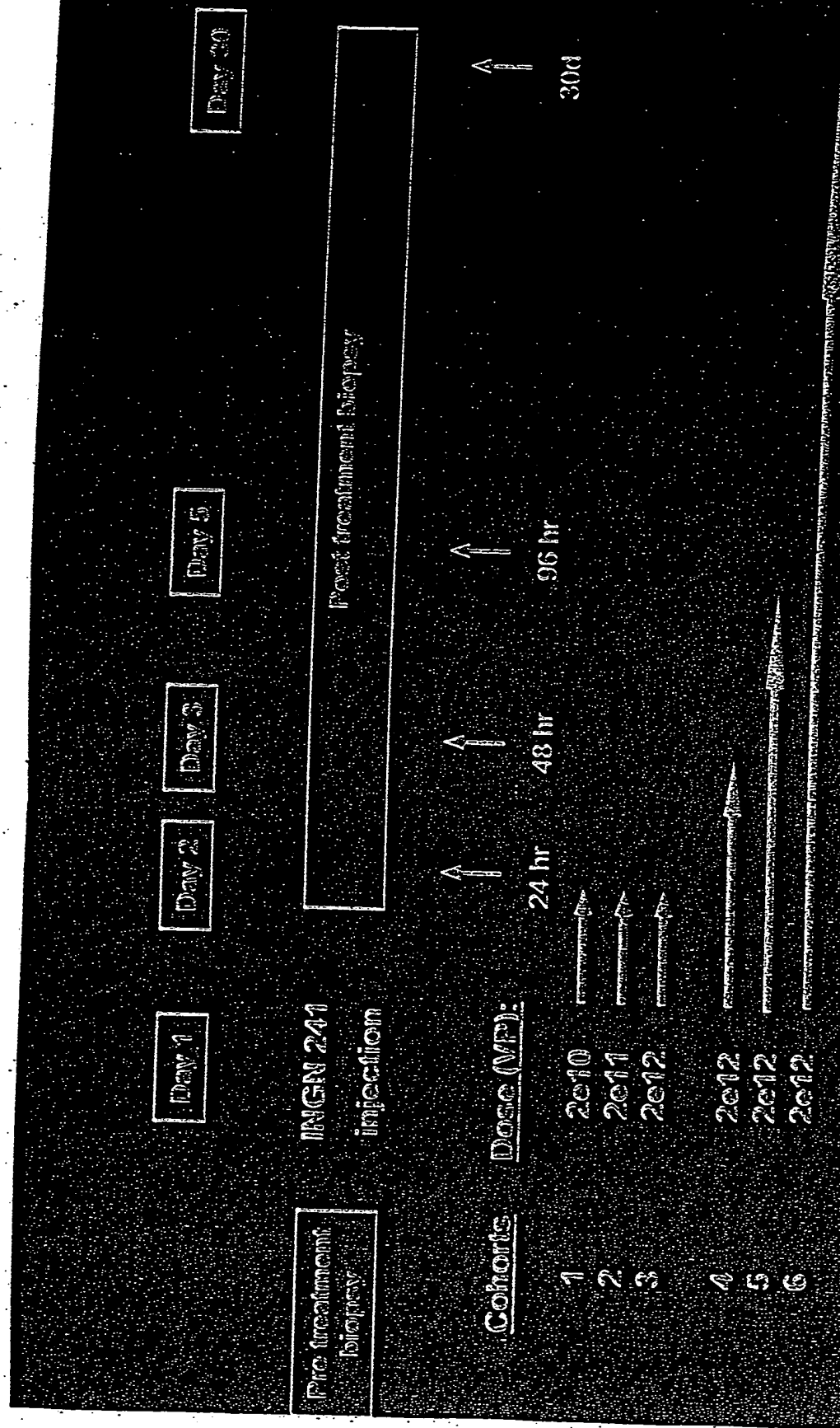
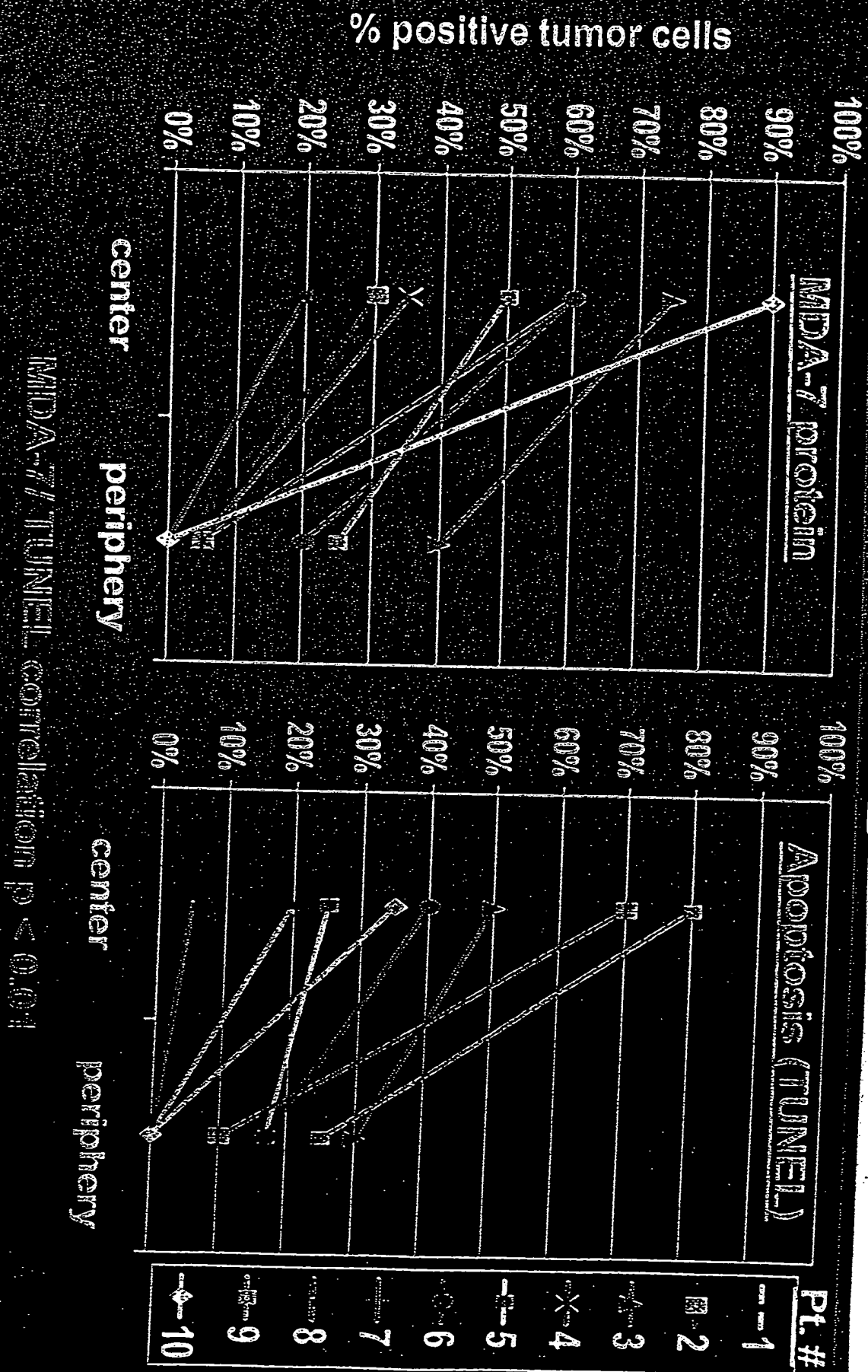
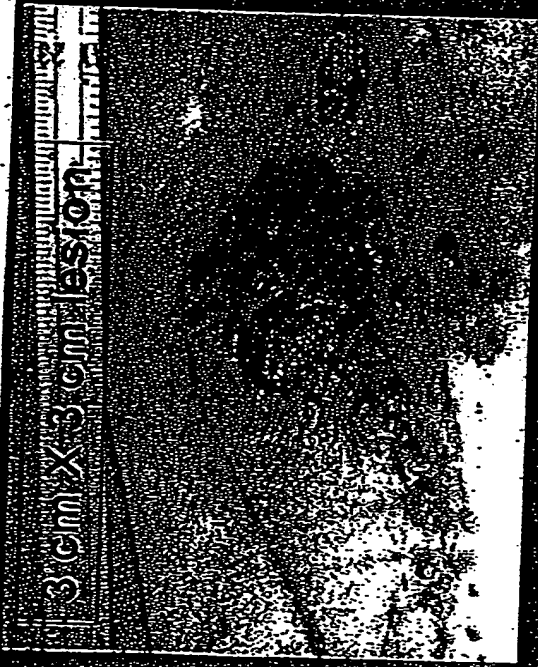


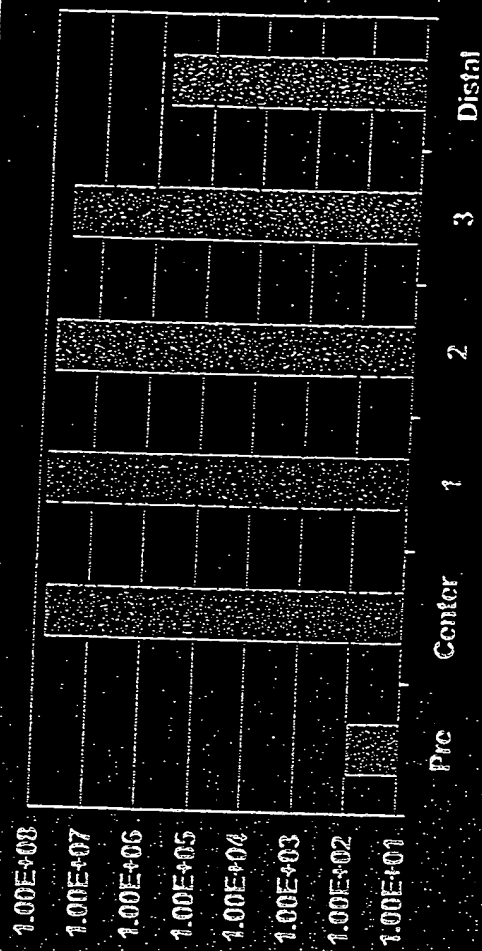
FIG. 35





Distance from center of lesion: 0 mm 3 6 9 12 mm

INGN 241
DNA
Expression
#copies/ug



MDA-7 protein expression

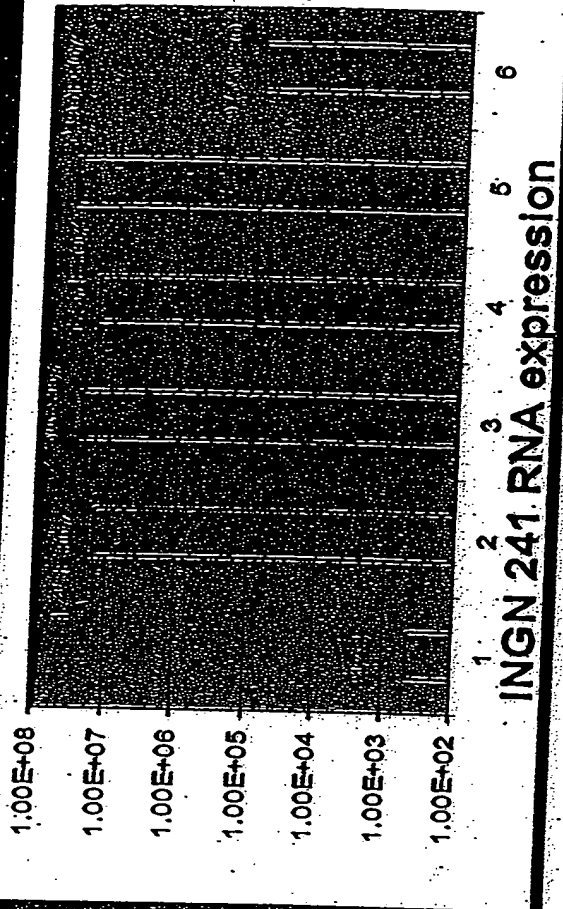
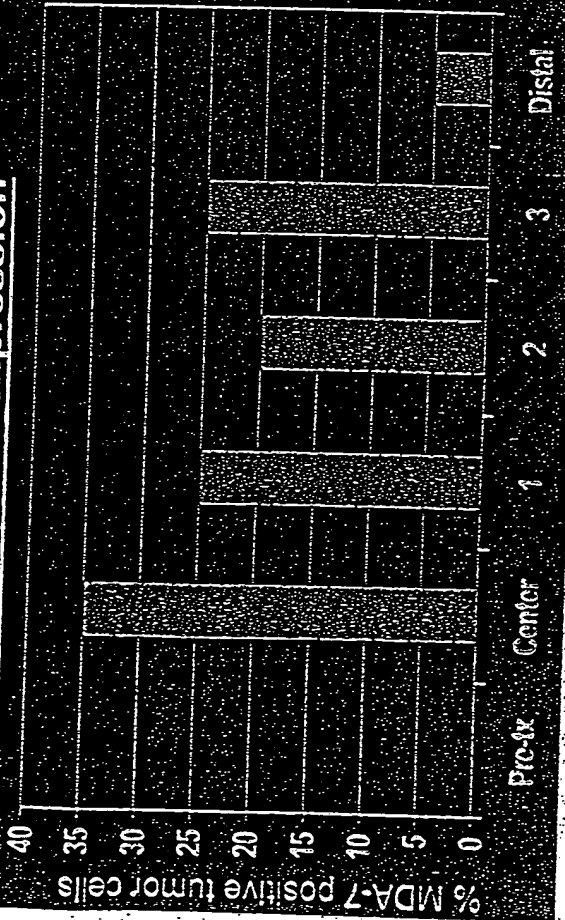


FIG. 36

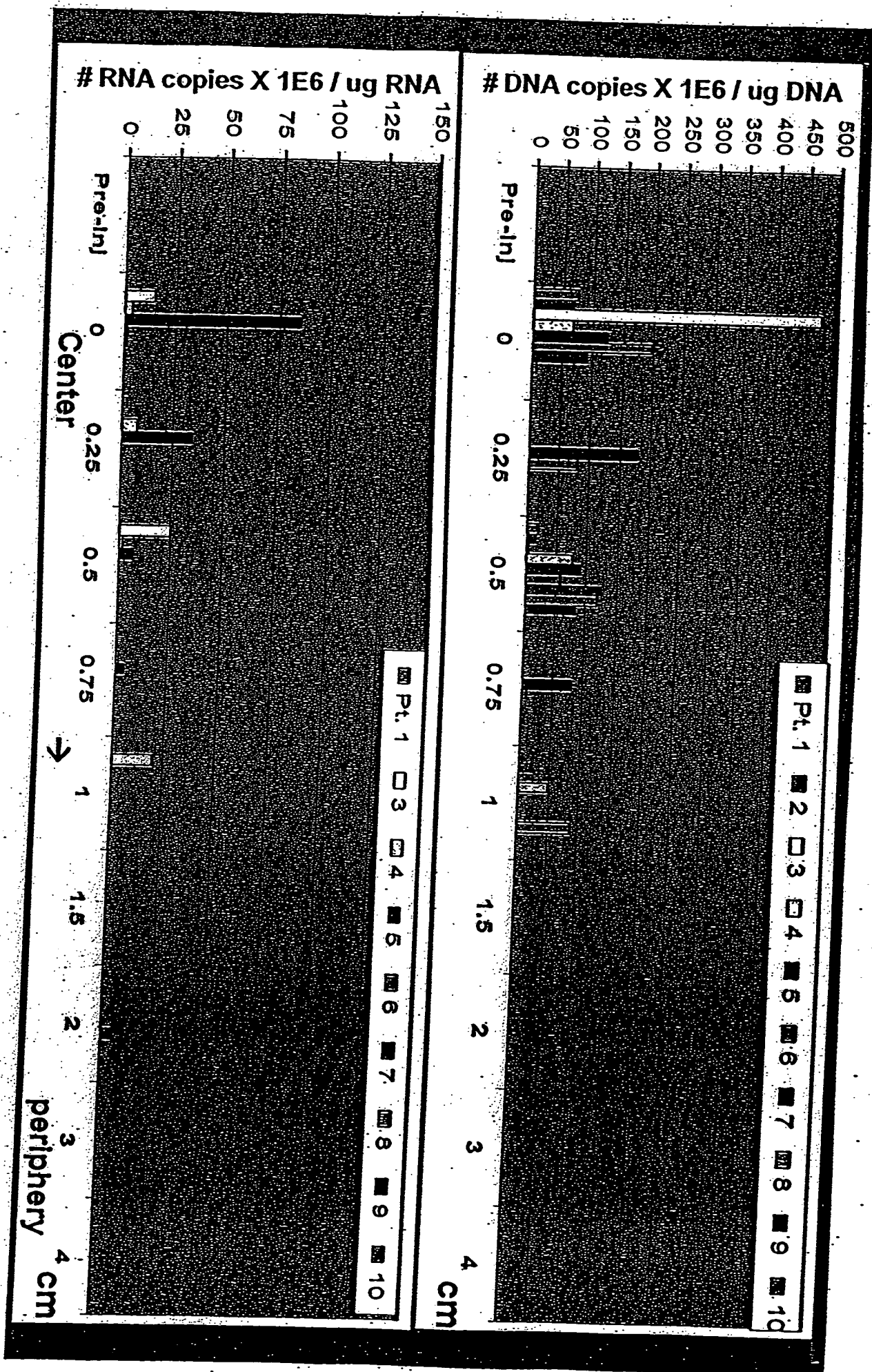
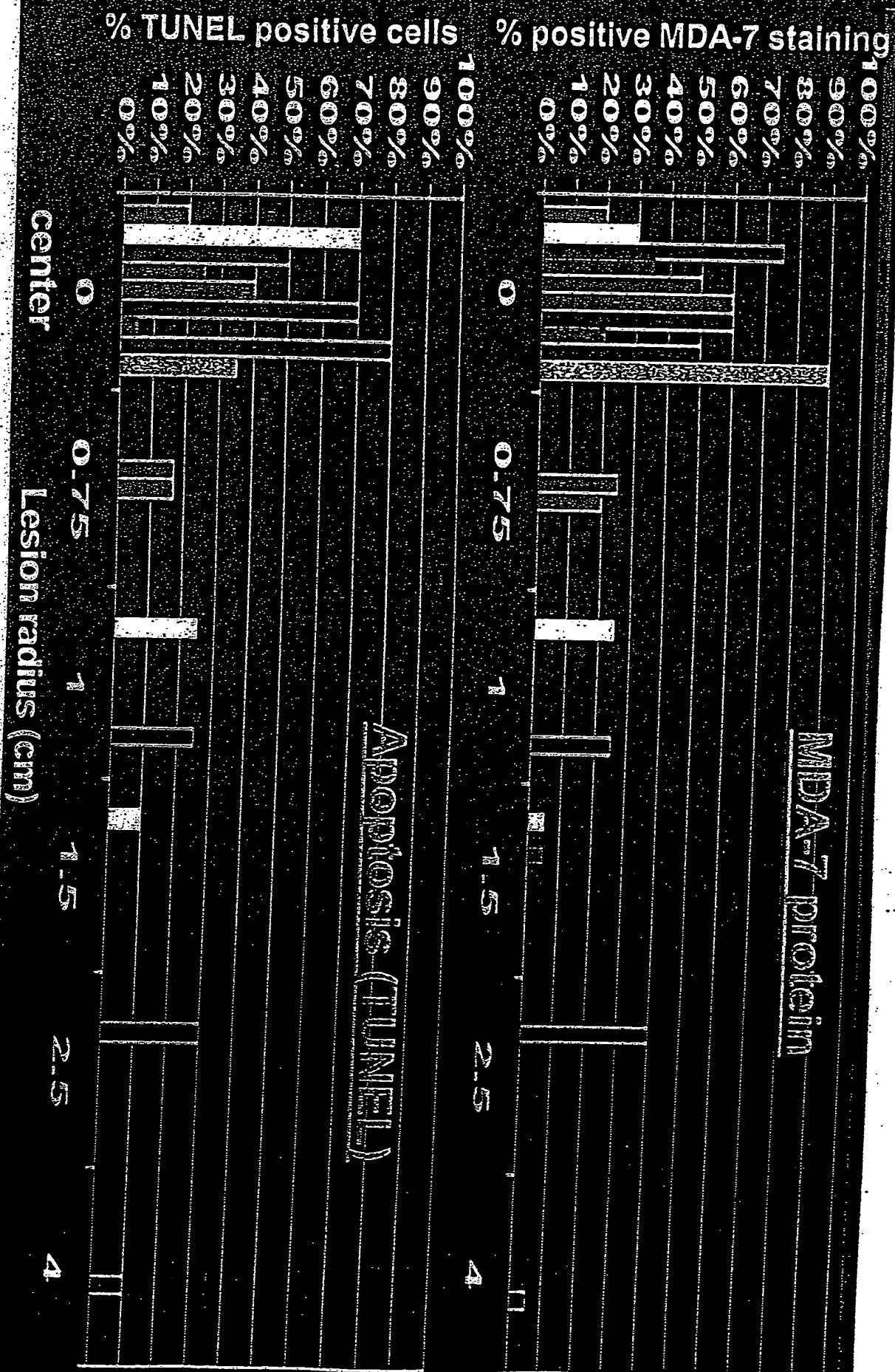


FIG. 37

FIG. 38



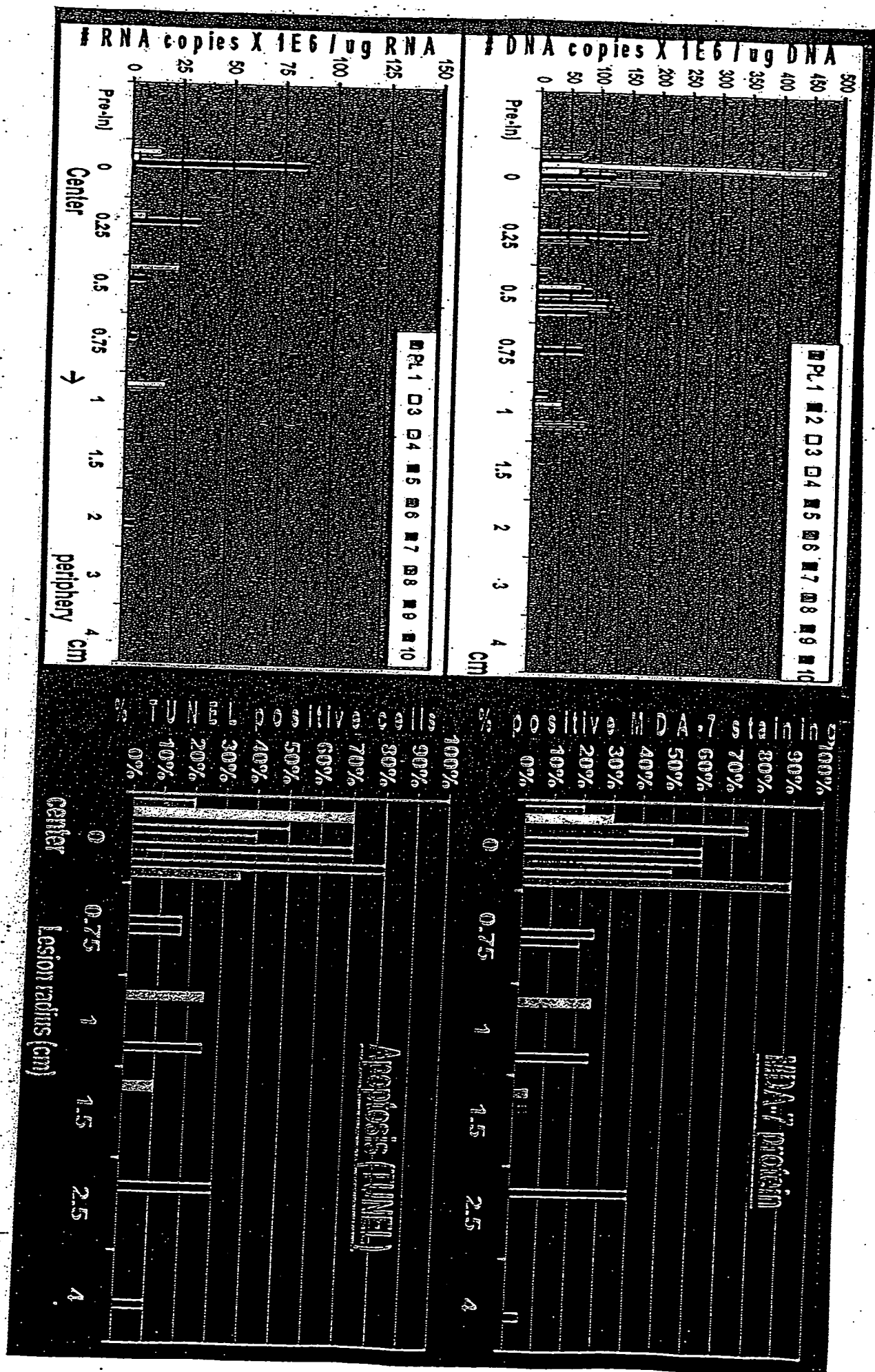


FIG. 39

Av. copies/cell: 0.001

740

900

1

0.04

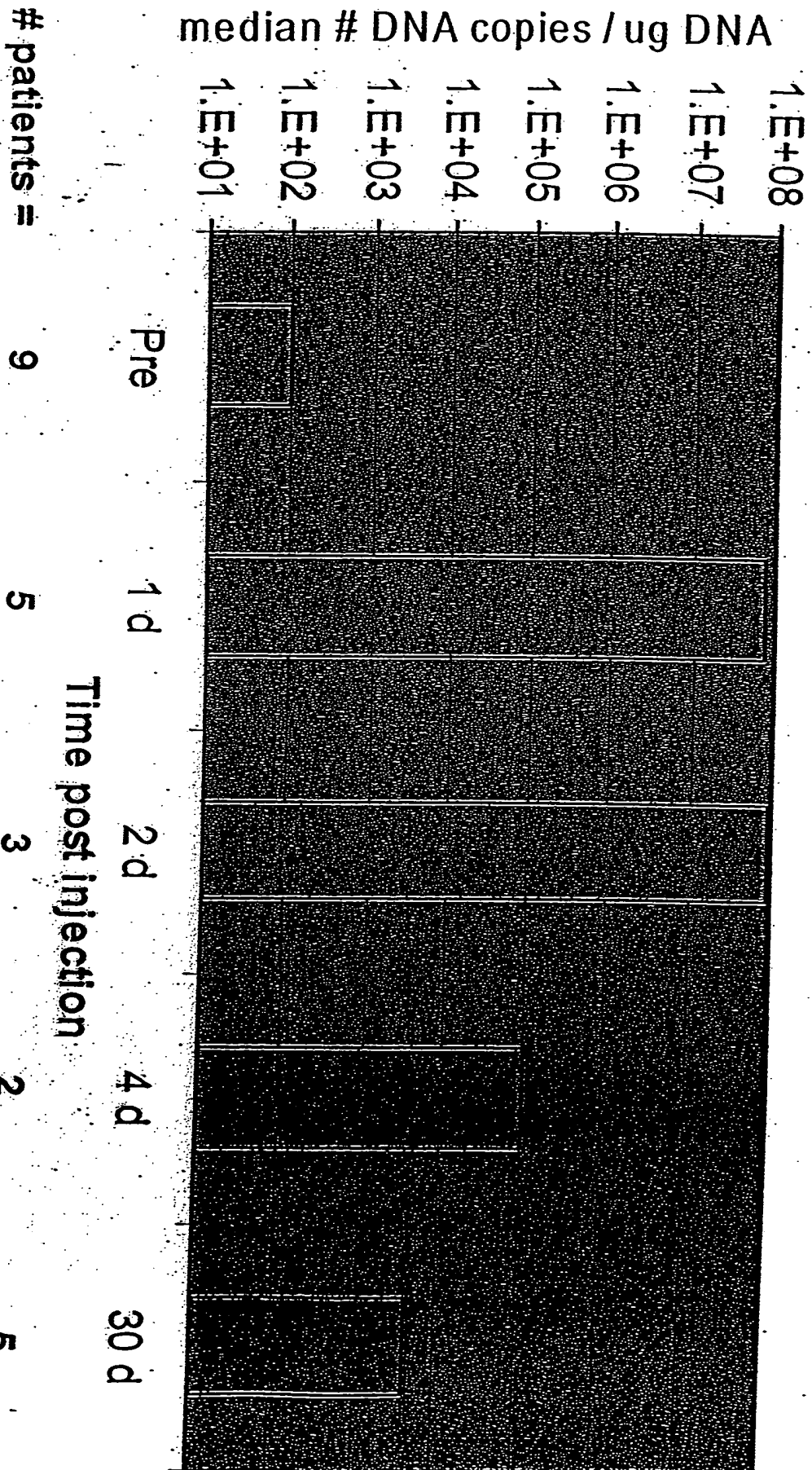


FIG. 40

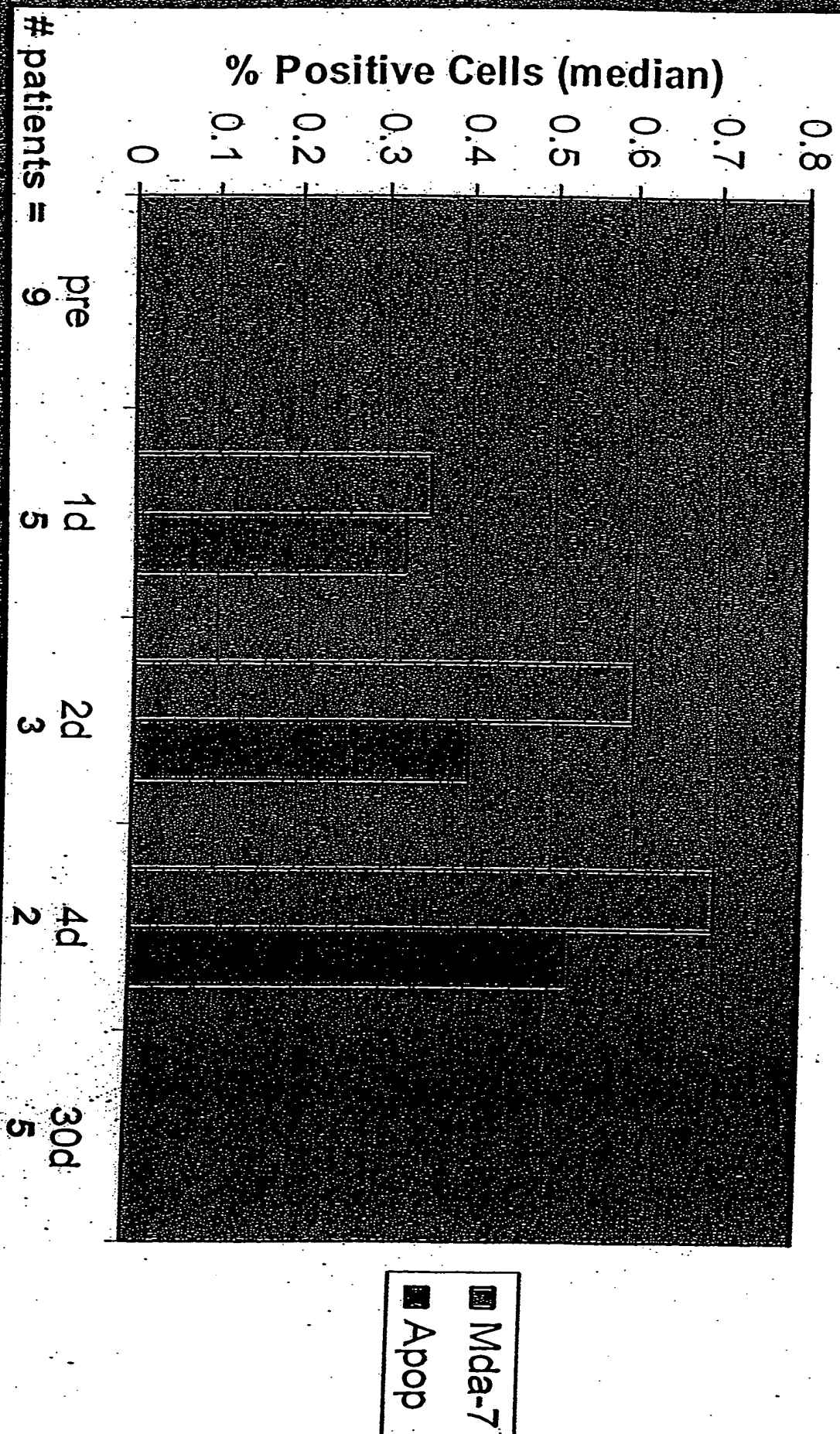


FIG. 41

FIG. 42

Single Dose (2E12 vp)

Patient	Primary Histology	# injections	Clinical Activity (Y/N)			Comment
			Local	Remote		
71	Renal Cell Ca	1	N	N		Withdrew prior to day 30
72	TCC Bladder	1	N	N		
73	Melanoma	1	N	N		
74	Colo-Rectal	1	N	N		
75	SCCHN	1	N	N		Withdrew prior to day 30
76	SCCHN	1	N	N		
77	SCCHN	1	N	N		
			N	N		

Repeat Dose (2E12 vp biweekly x3)

81	AdenoCa	3	-	-		Withdrew
83	Melanoma	12	Y*	Y**		CR
84	Melanoma	12	N	N		Stable Disease
85	SCCHN	6	Y	N		Central necrosis
86	NSCLC	3	-	-		Not eval
87	SCCHN	6	Y	pending		On study
88	Melanoma	6	Y	pending		On study

* Three lesions treated consecutively: pCR in 1st, clinCR in 2nd, regression in 3rd

** marked erythema around remote cutaneous lesion

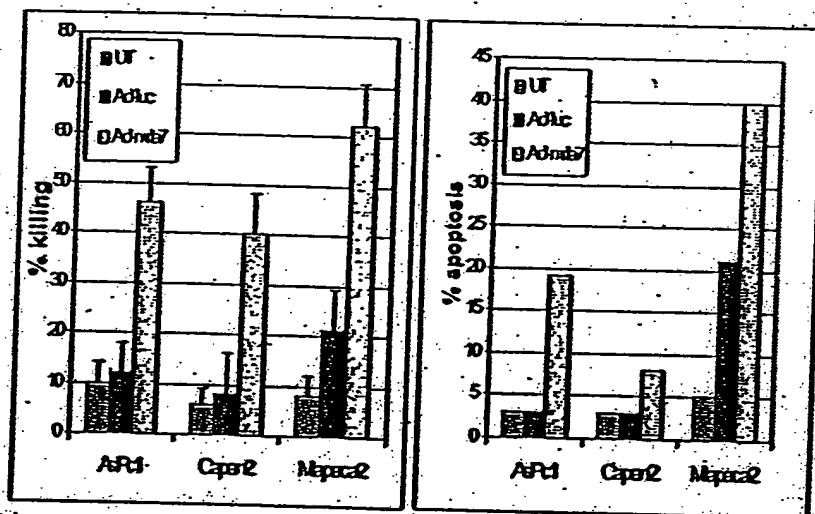


FIG. 43

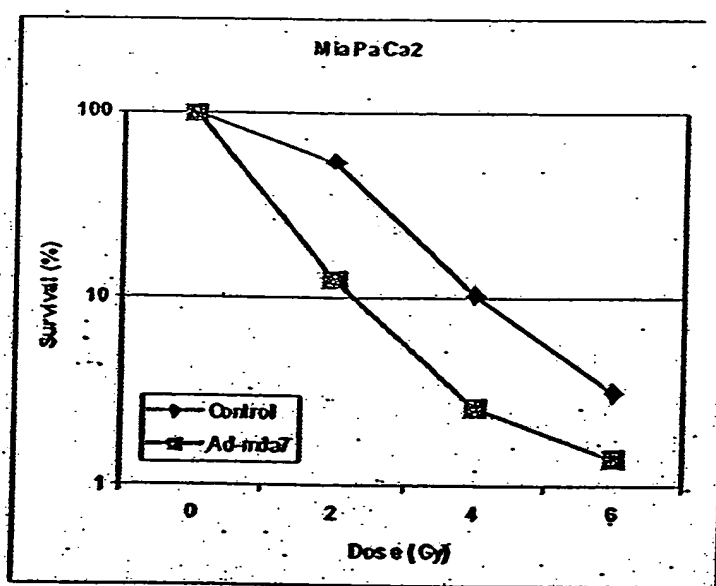


FIG. 44

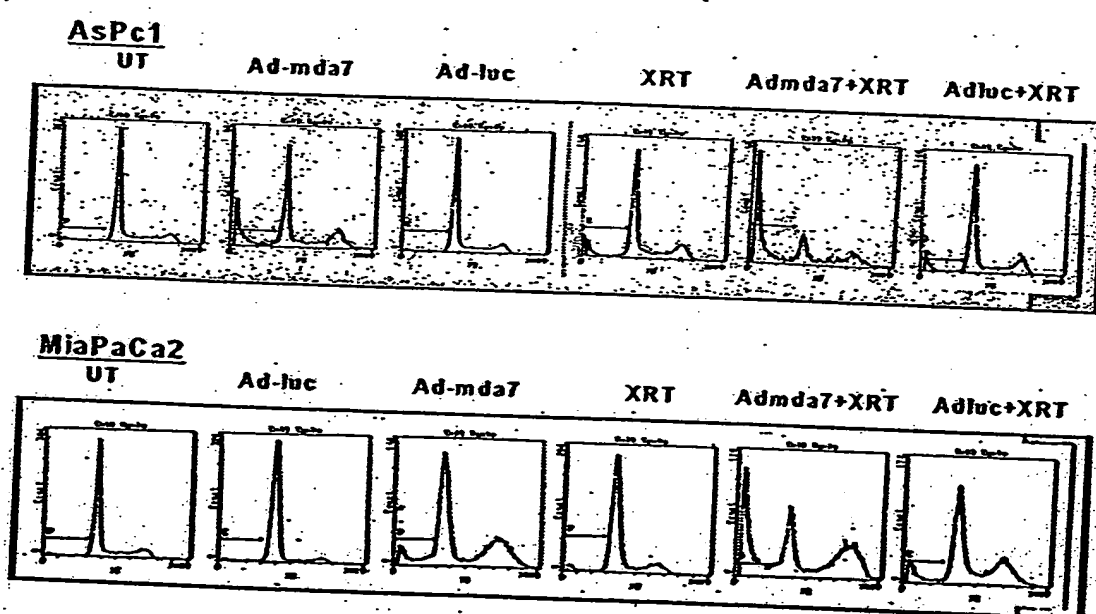


FIG. 45

48 hrs after infection

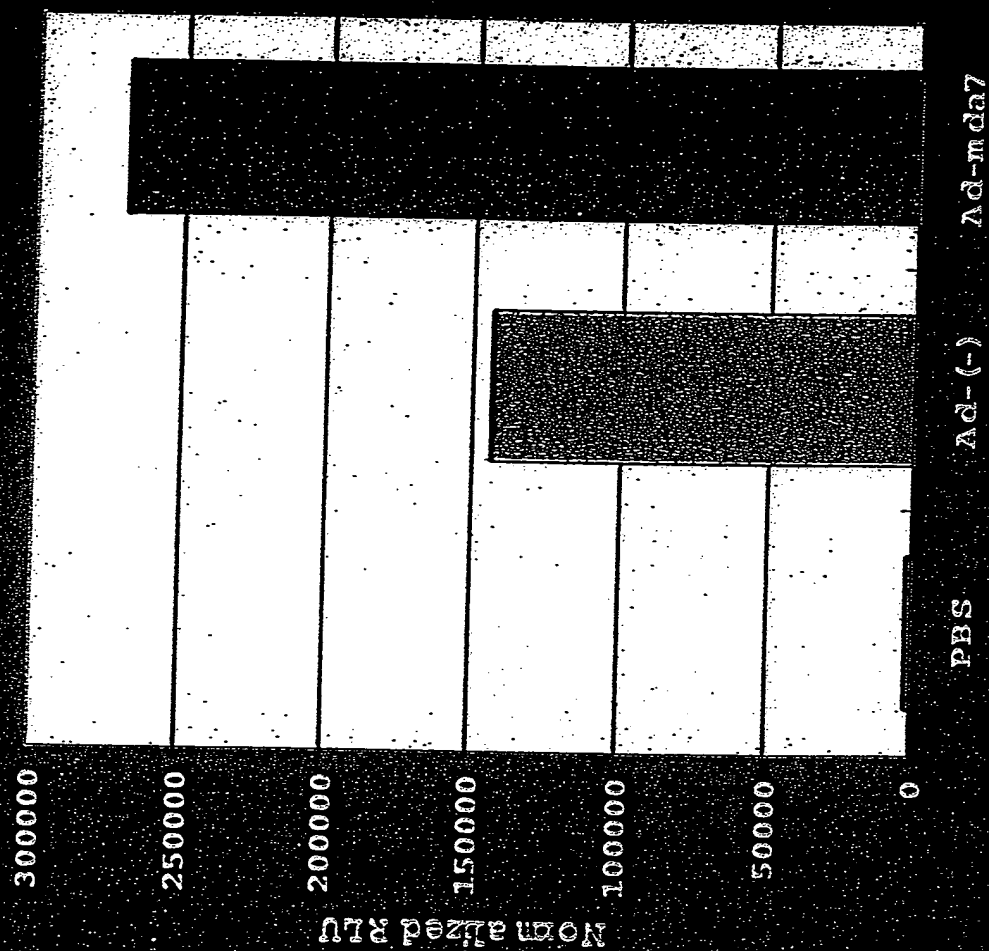


FIG. 46

H1299



Parental neo clone 1 clone 2 clone 3

IC50 value

Ad-mda7

clone	($\times 10^3$ vp/cell)
neo	3.27 ± 1.1
clone 1	2.58 ± 1.25
	1.25 ± 0.3
clone 3	3.98 ± 0.88

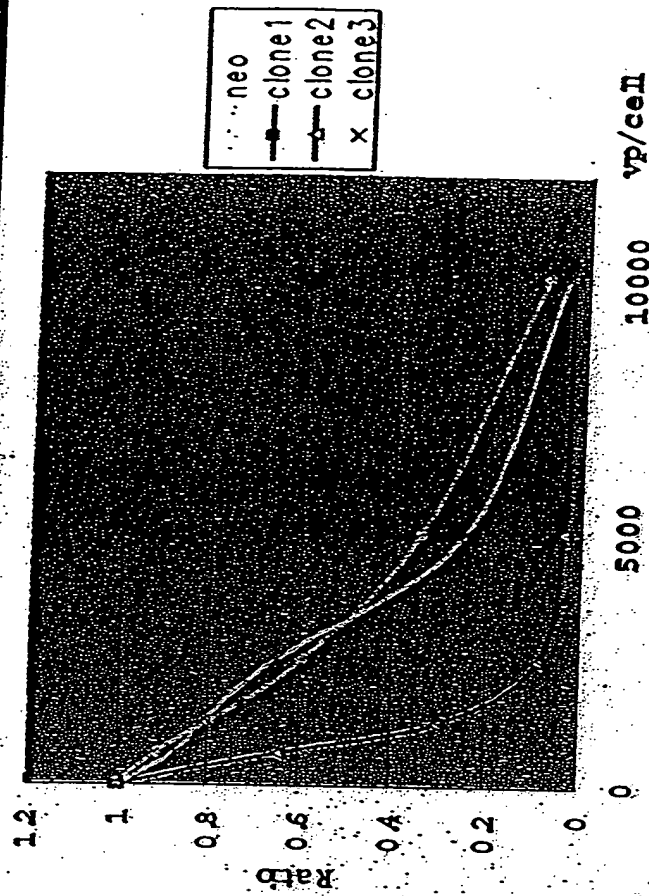


FIG. 47

H1299

72hrs after infection

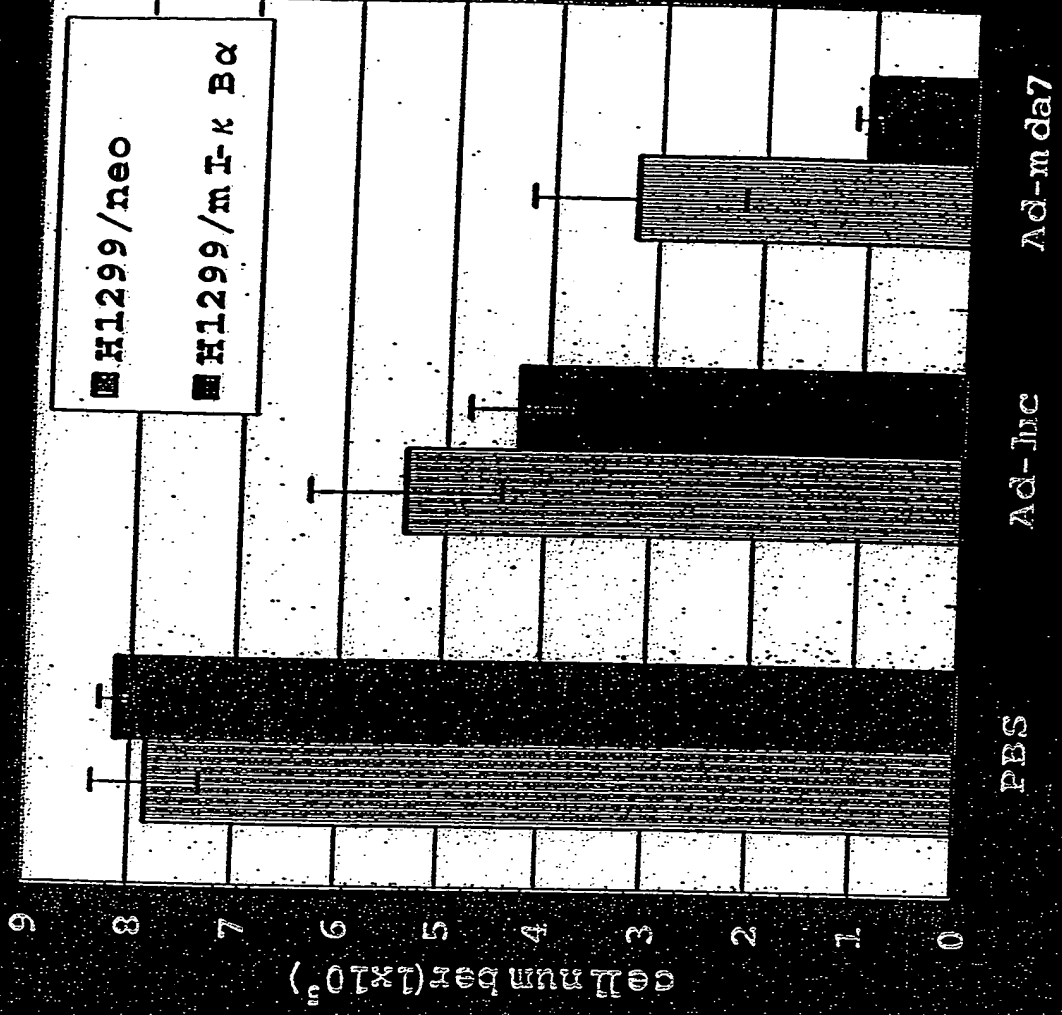
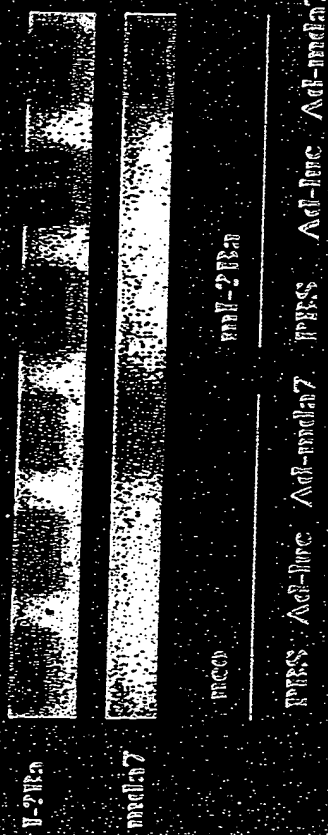


FIG. 48

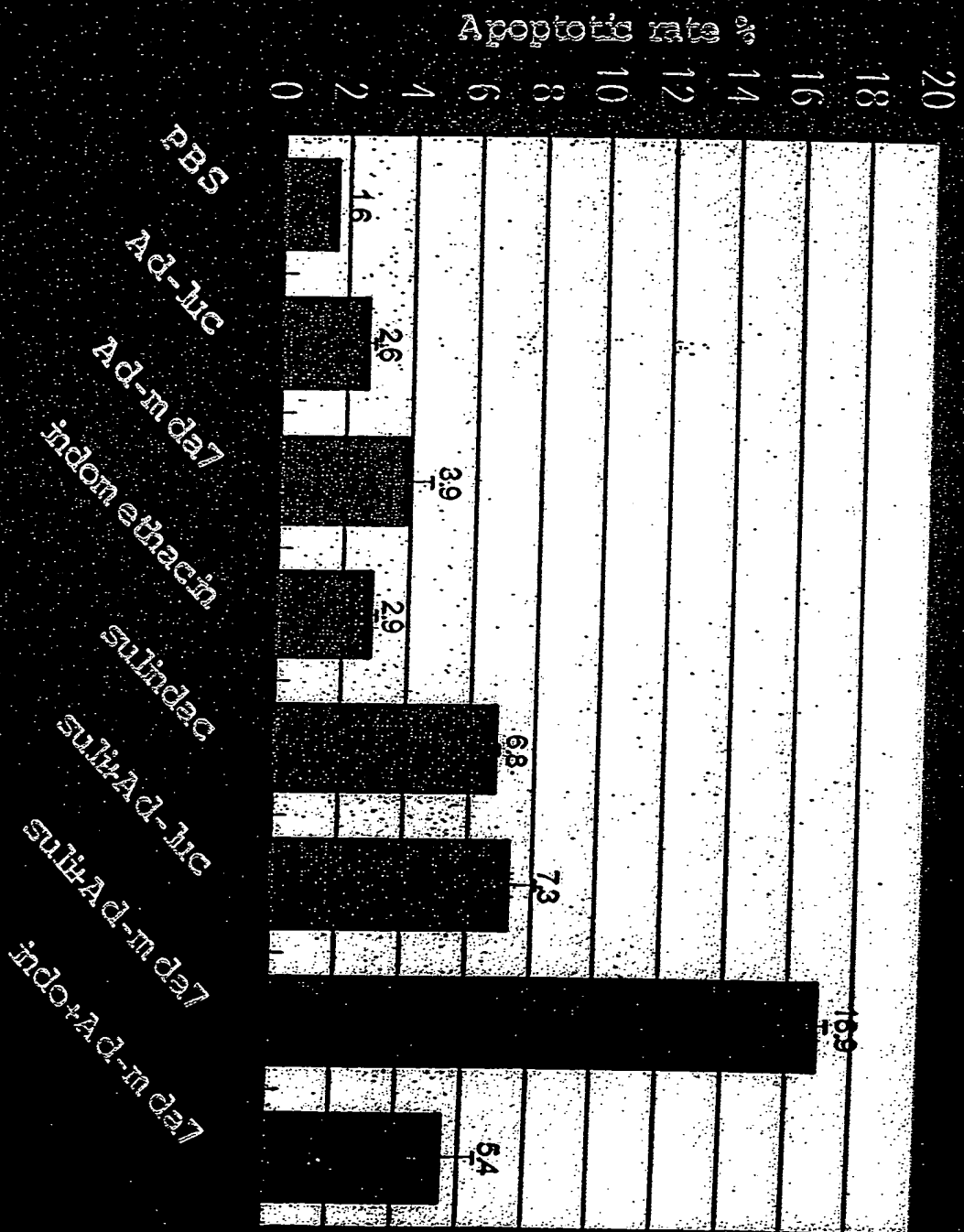


FIG. 49A

A

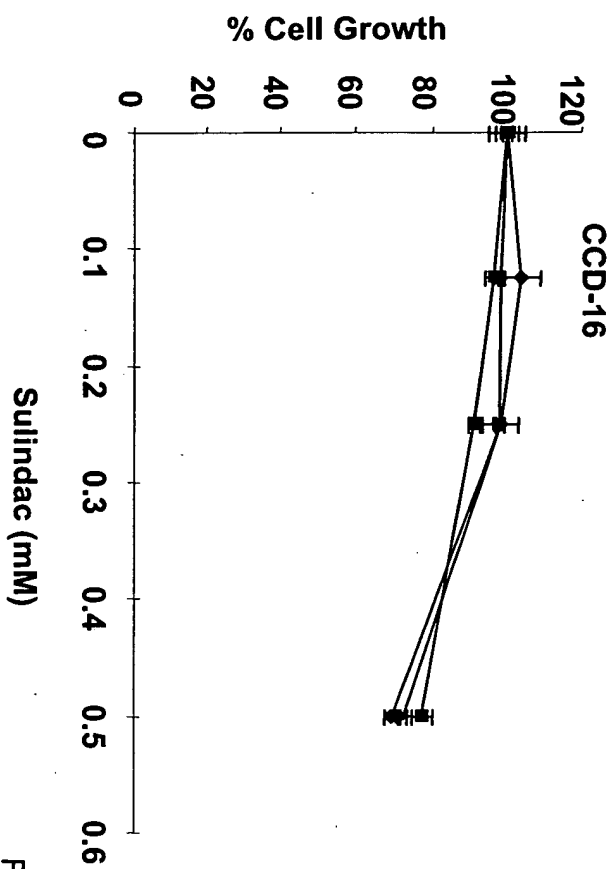
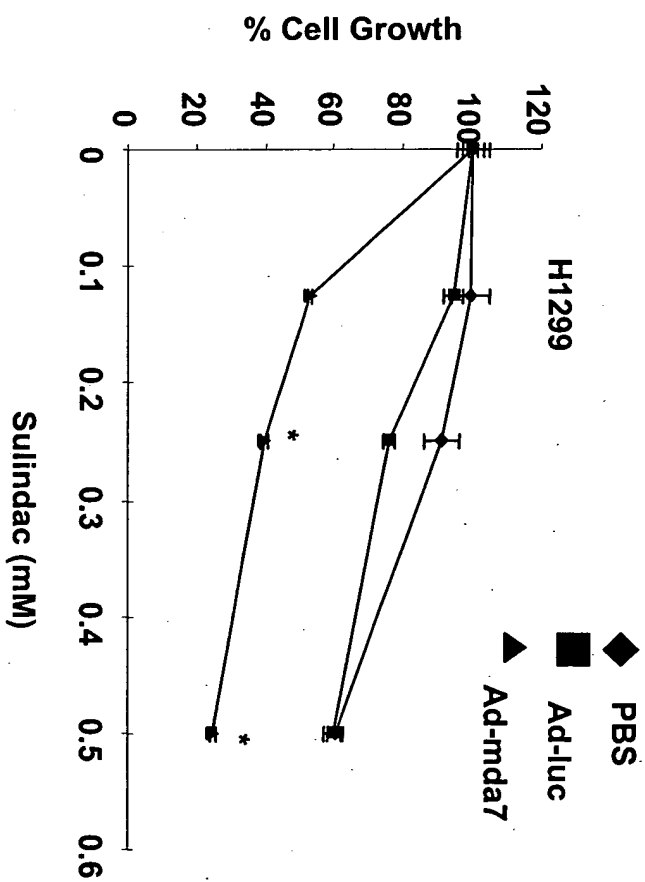
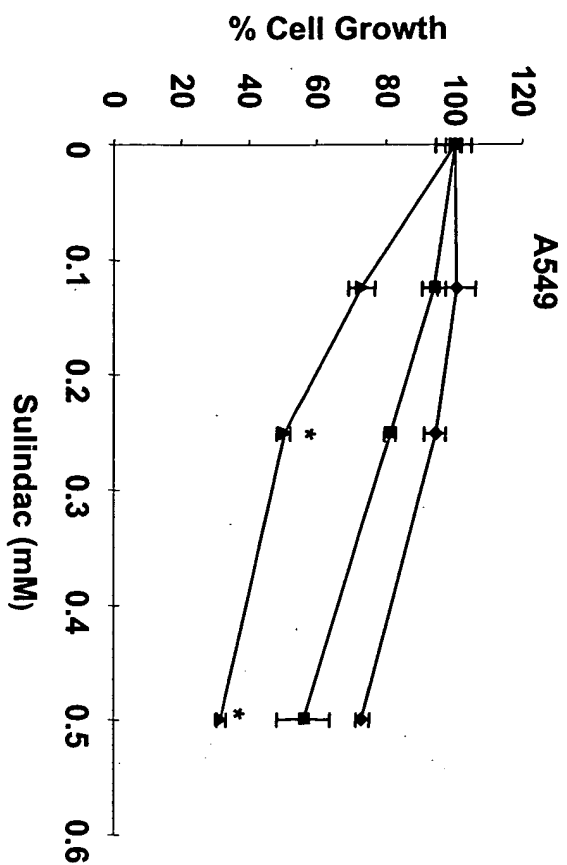


FIG. 49B

B

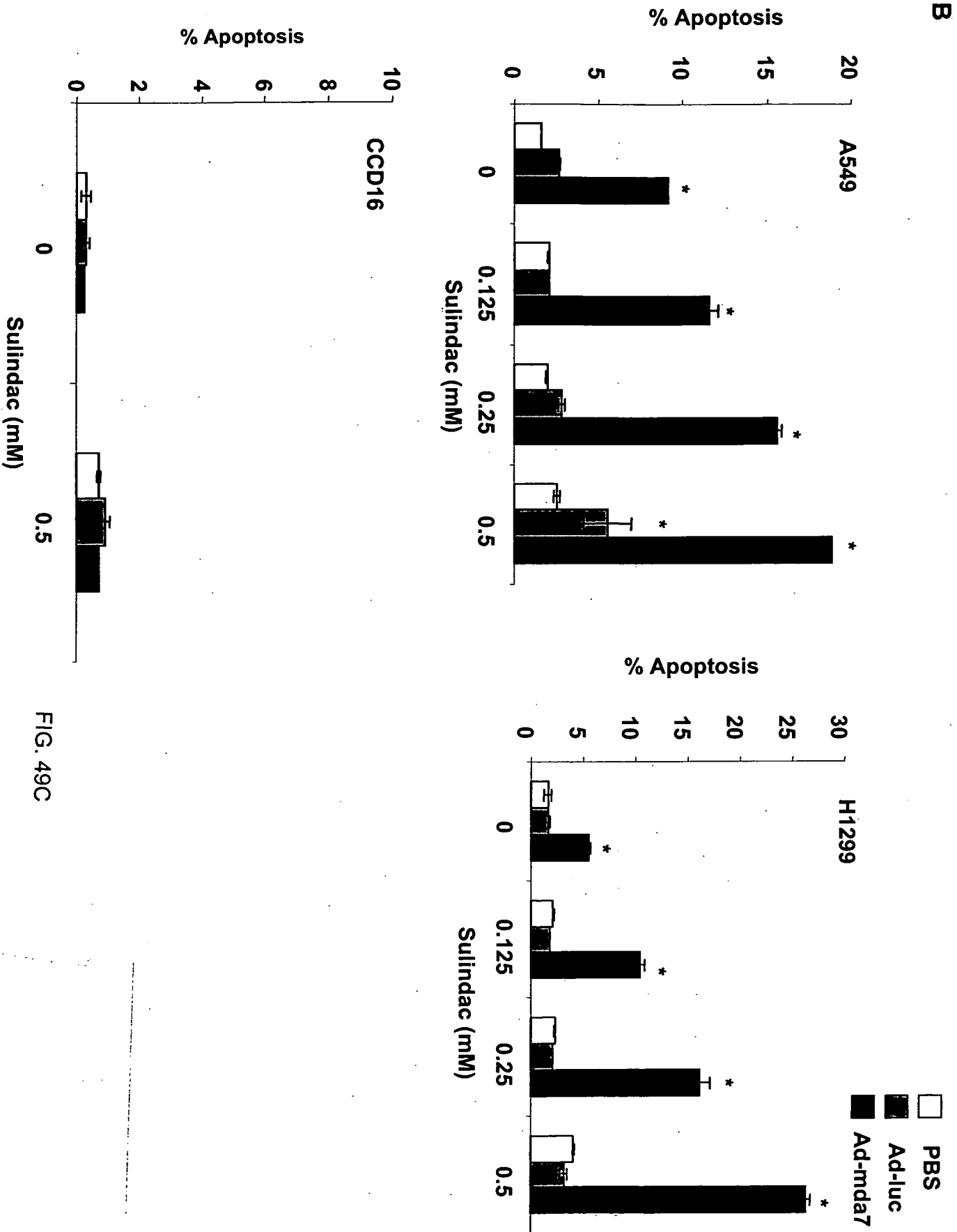


FIG. 49C

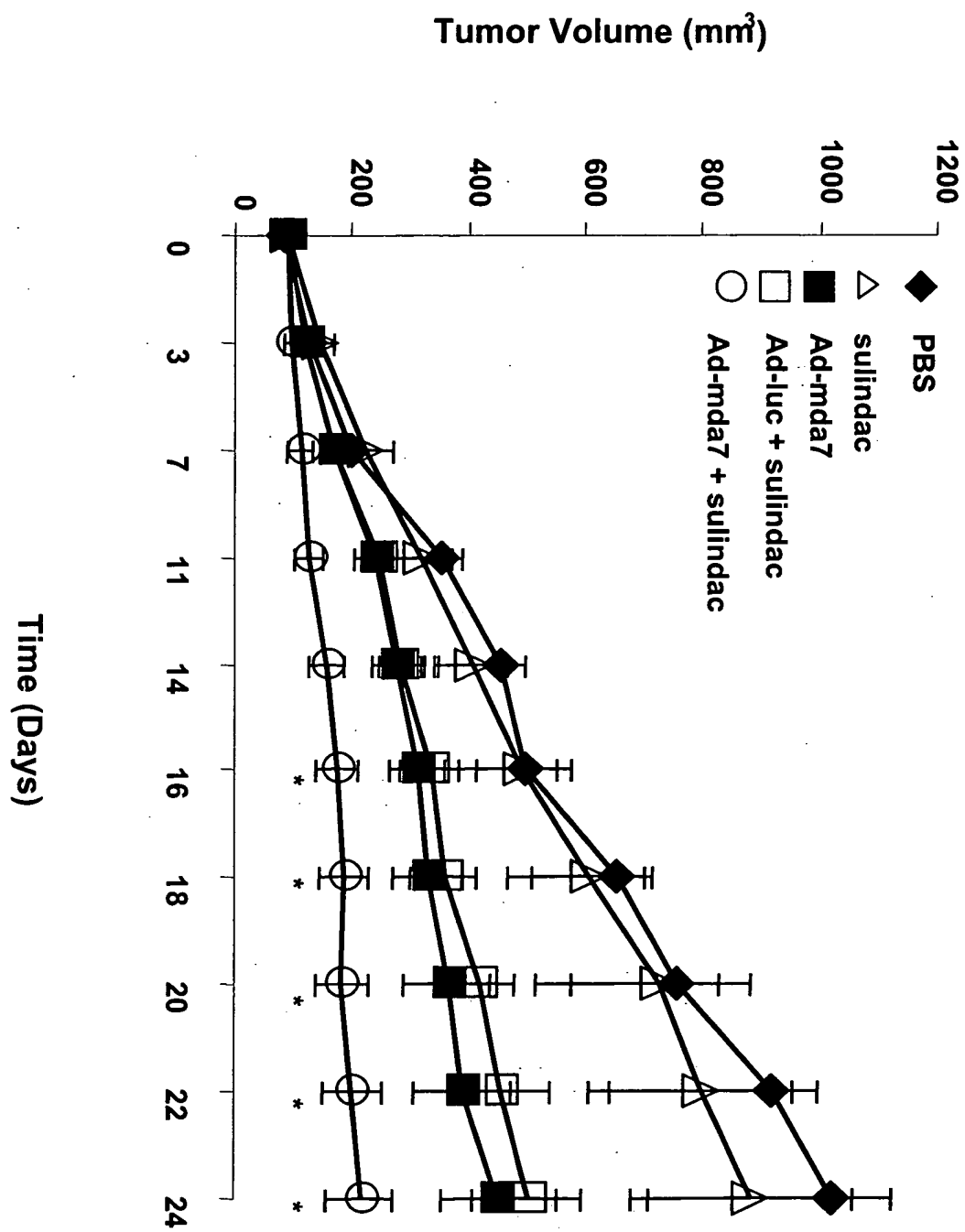


FIG. 49D

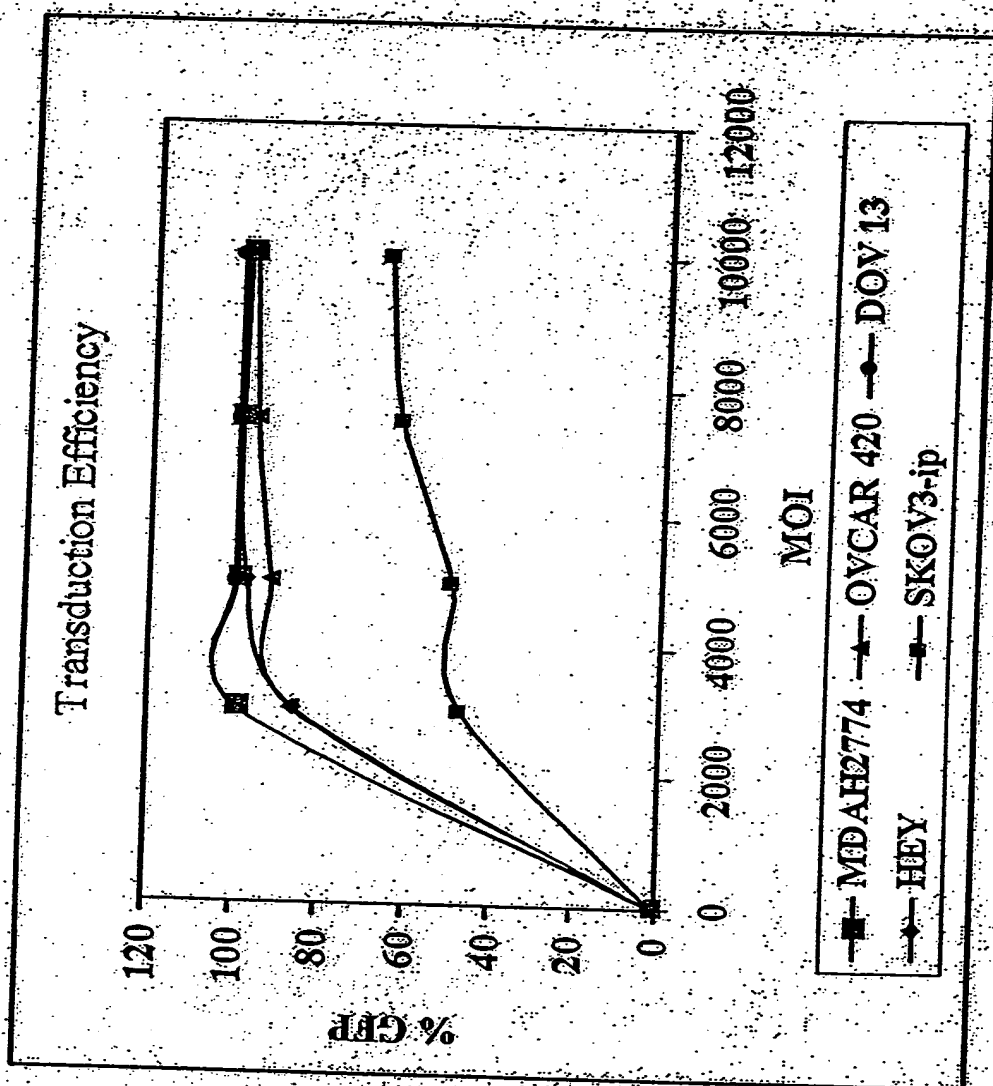


FIG. 50

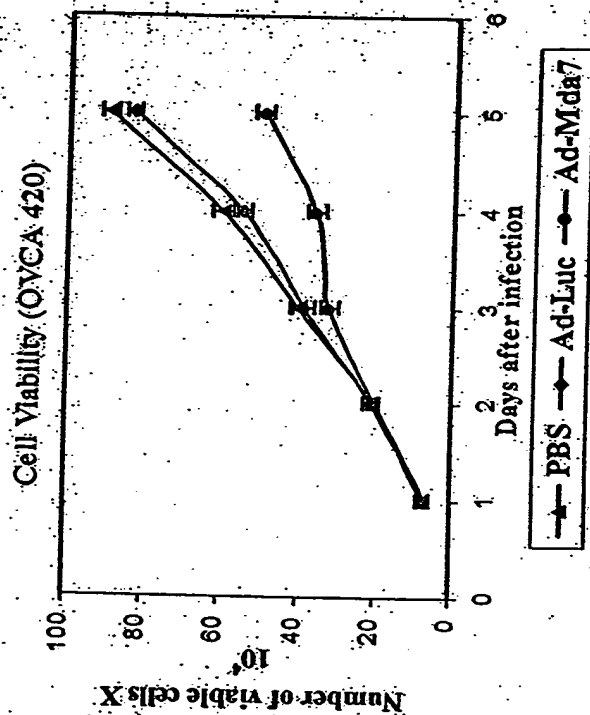
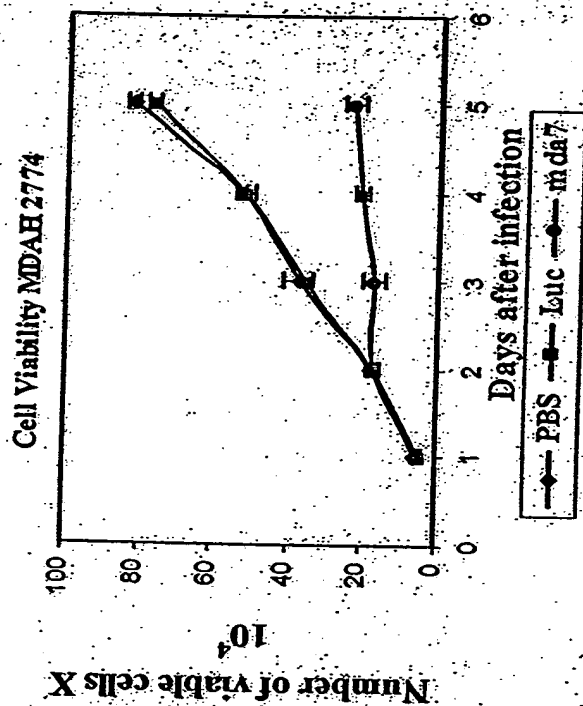


FIG. 51

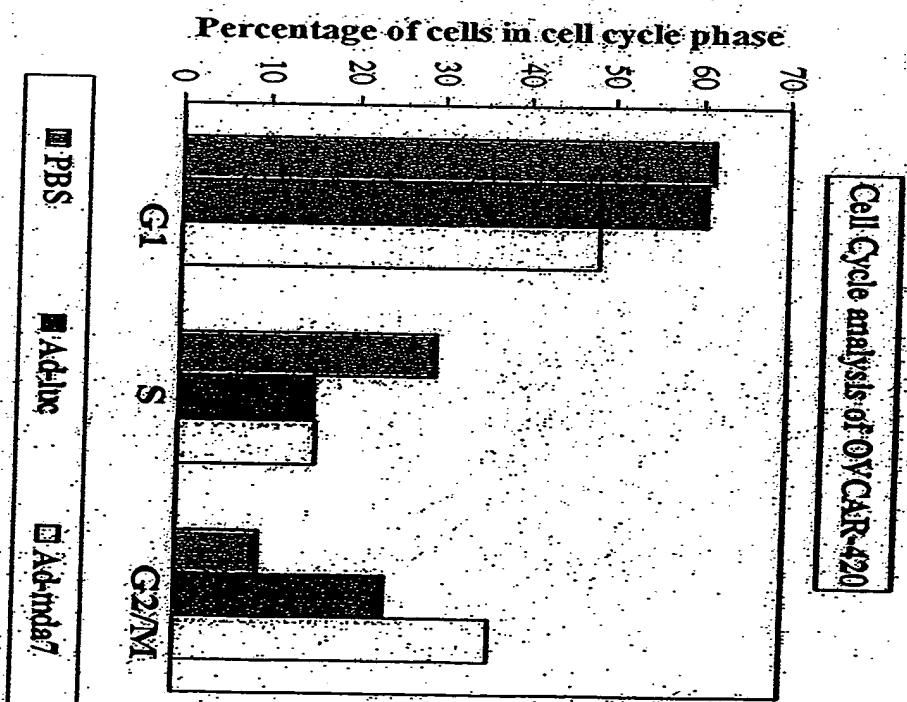
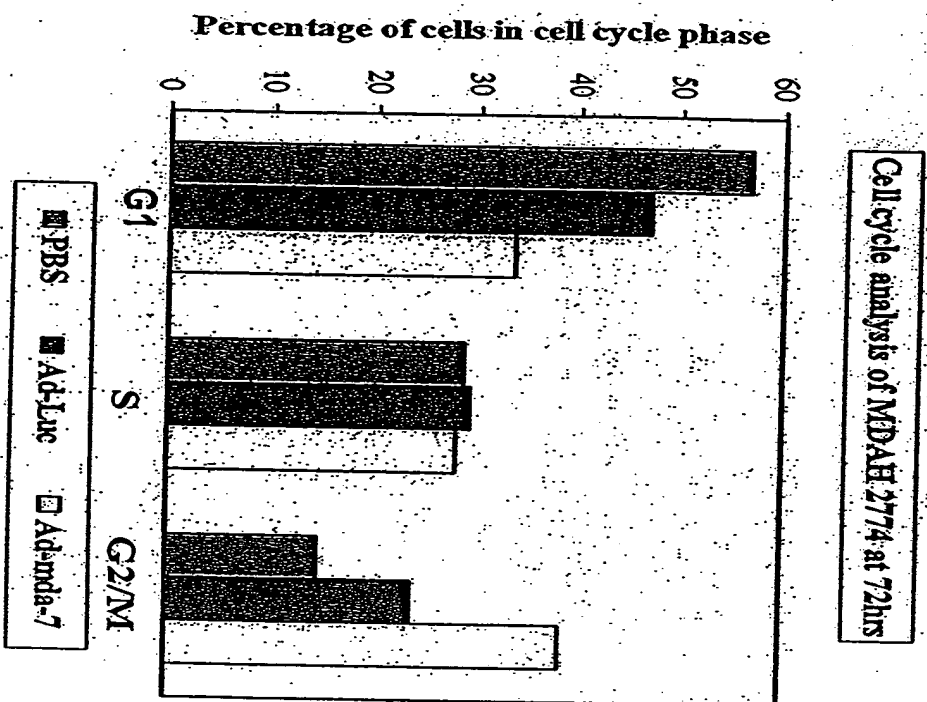


FIG. 52

Cell Survival in MDA-MB-486

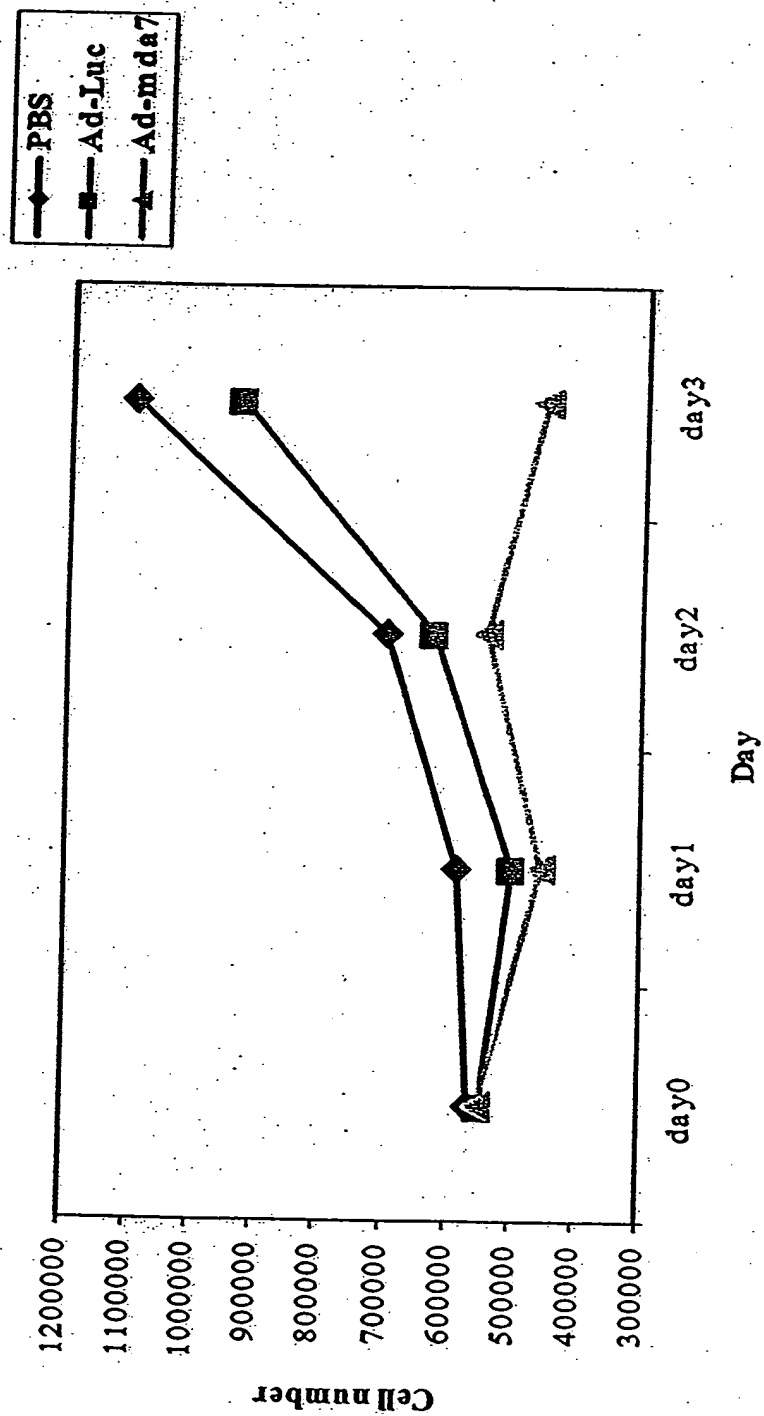


FIG. 53

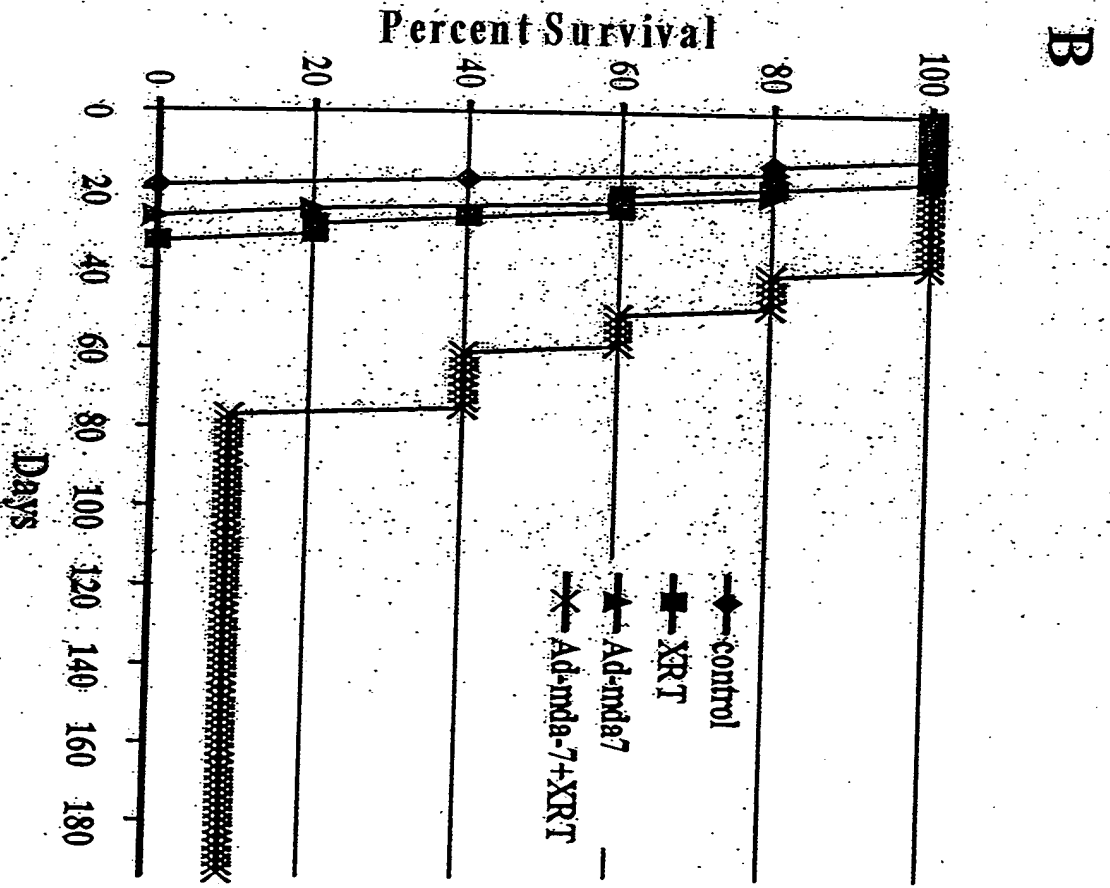
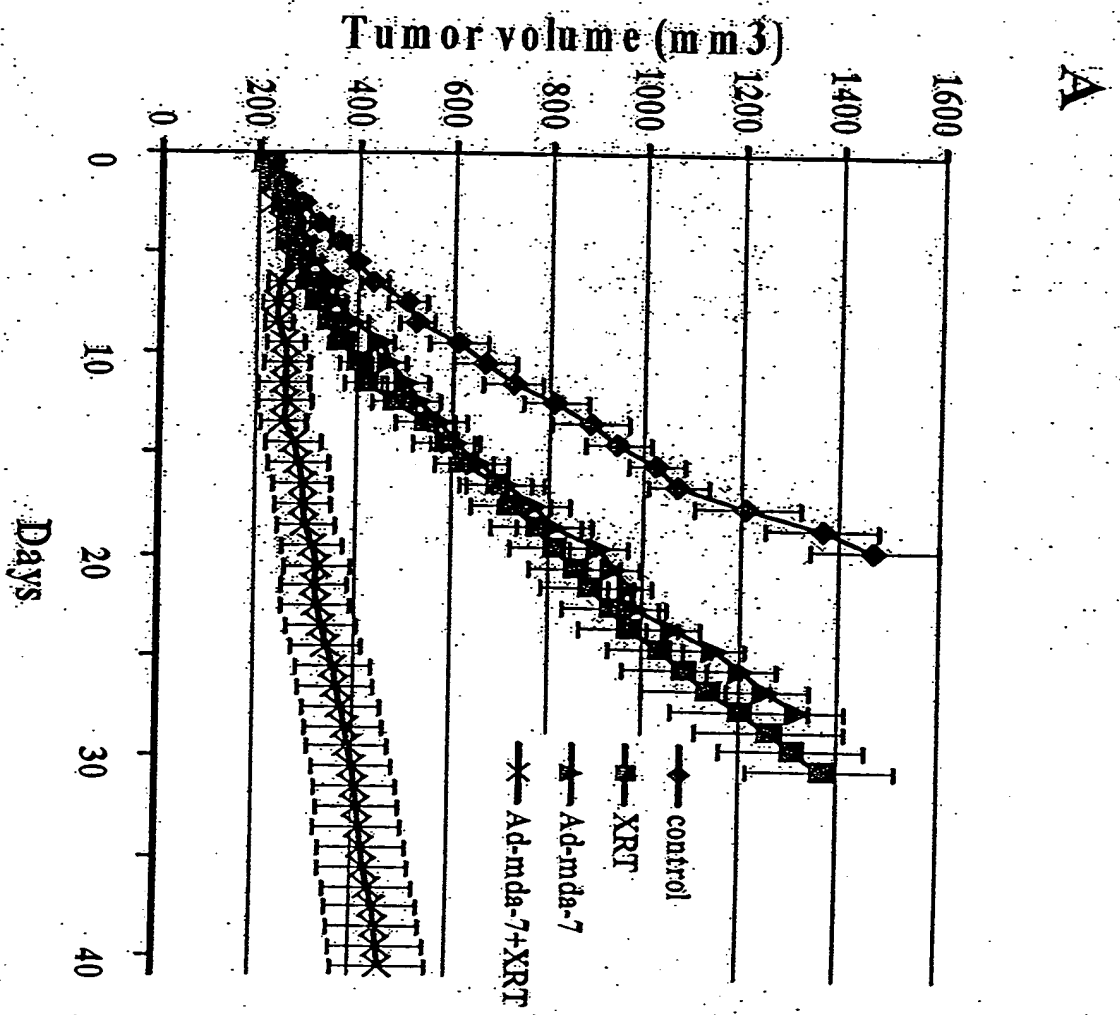


FIG. 54

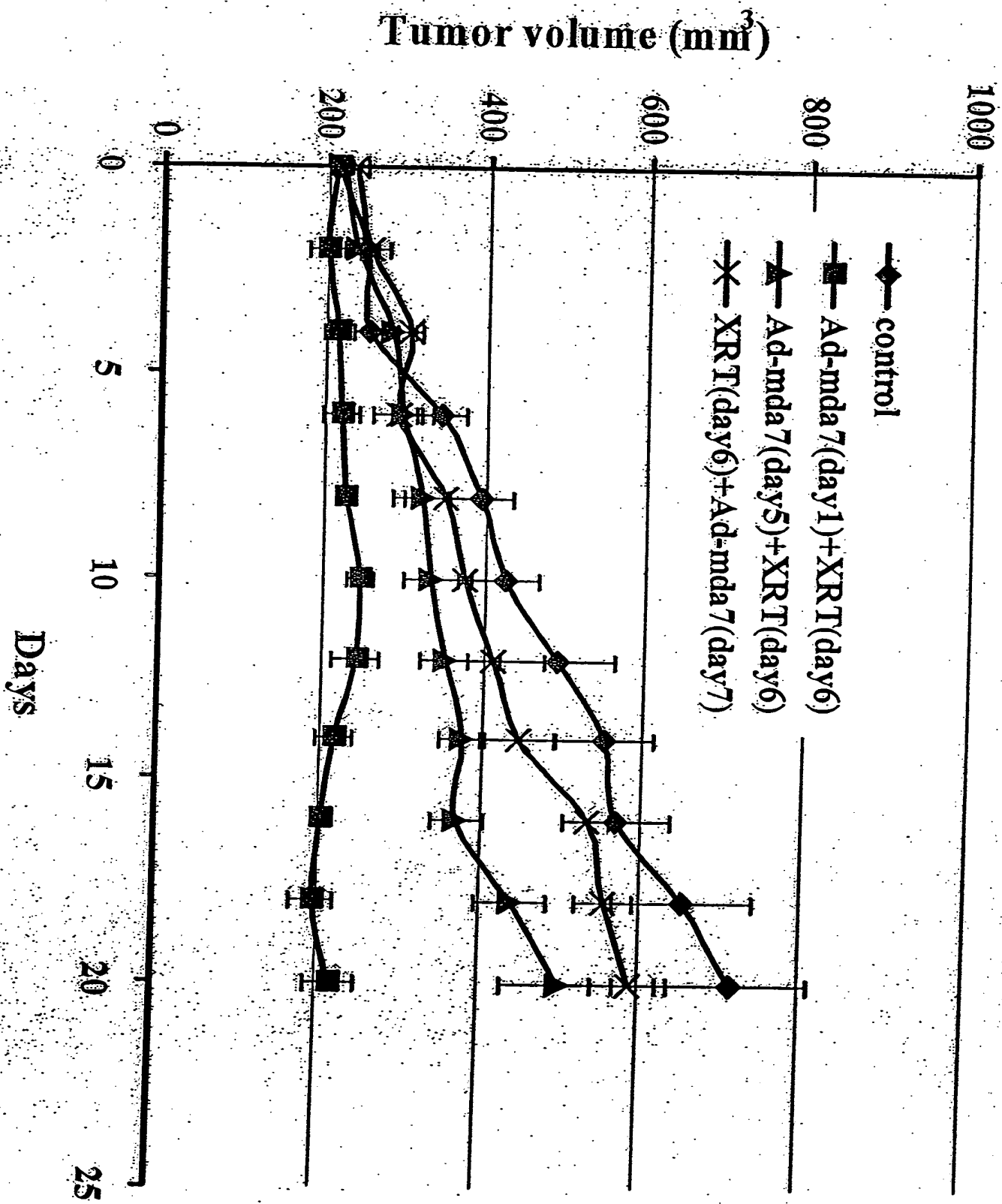


FIG. 55

B

Apoptotic Index

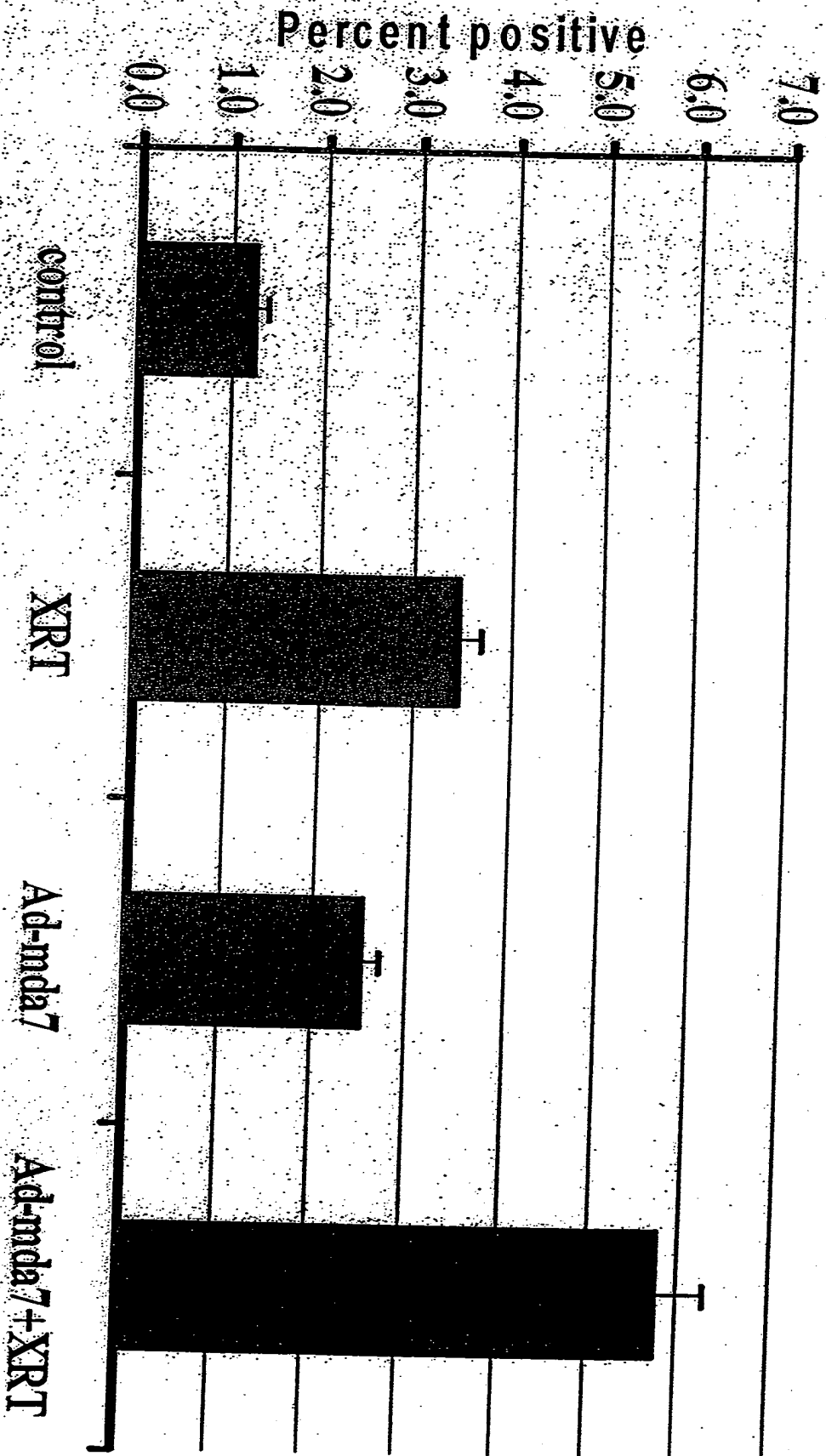
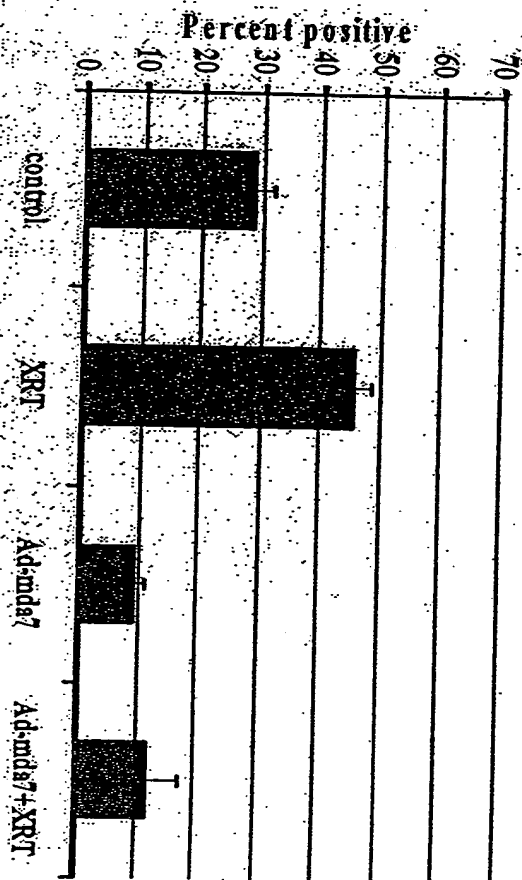


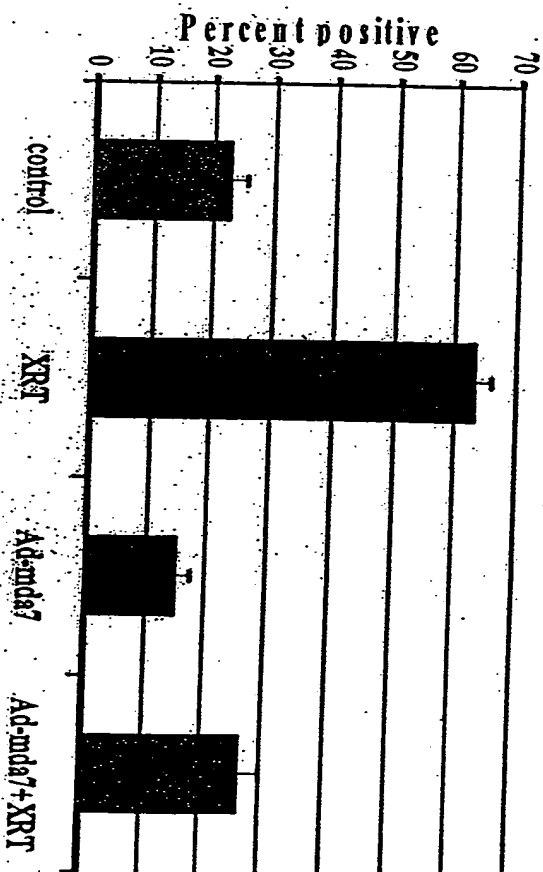
FIG. 56

A **VEGF**



B

bFGF



C

IL-8

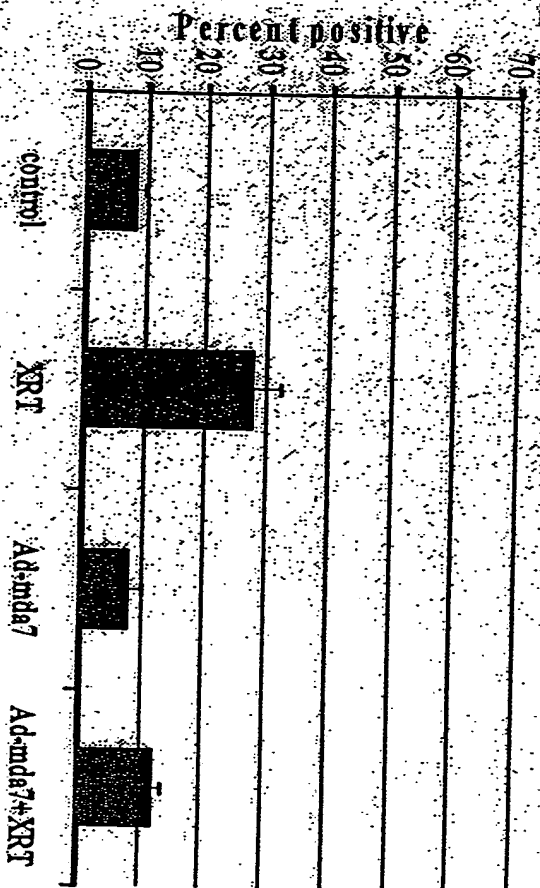


FIG. 57

Micro Vessel Density

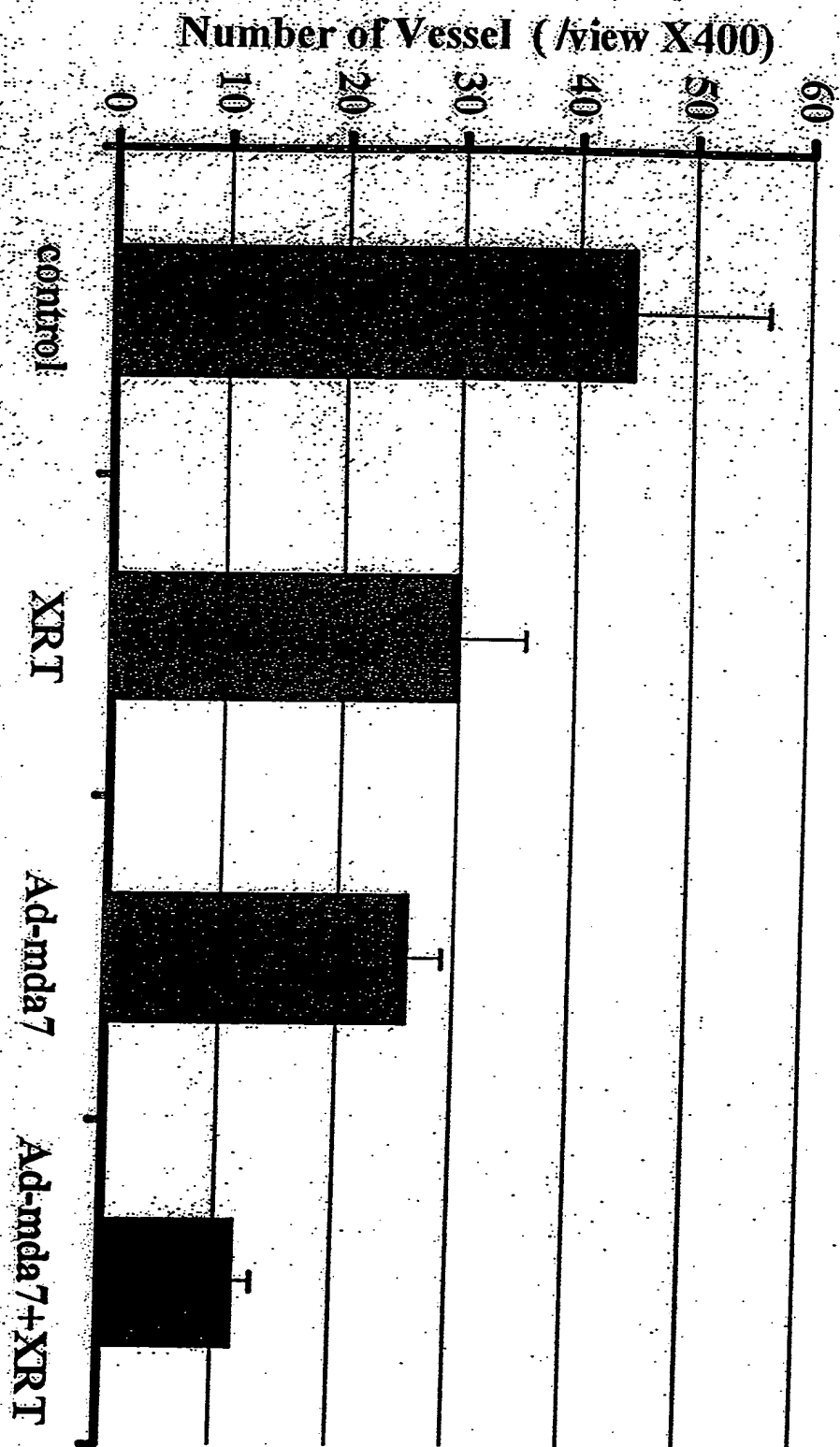
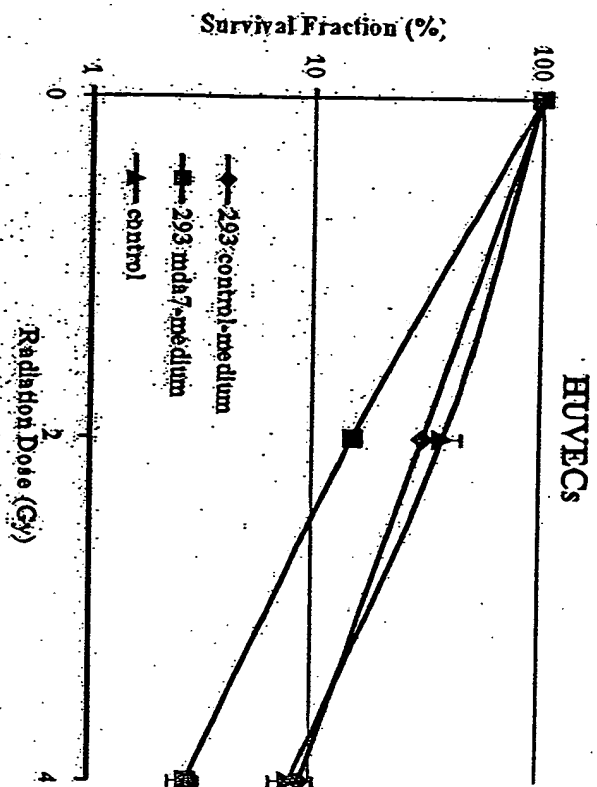
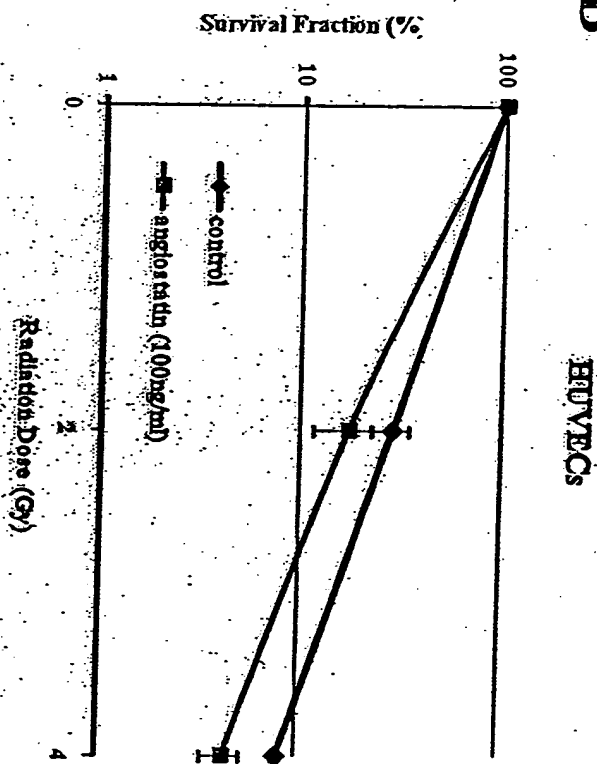


FIG. 58

A



B



C

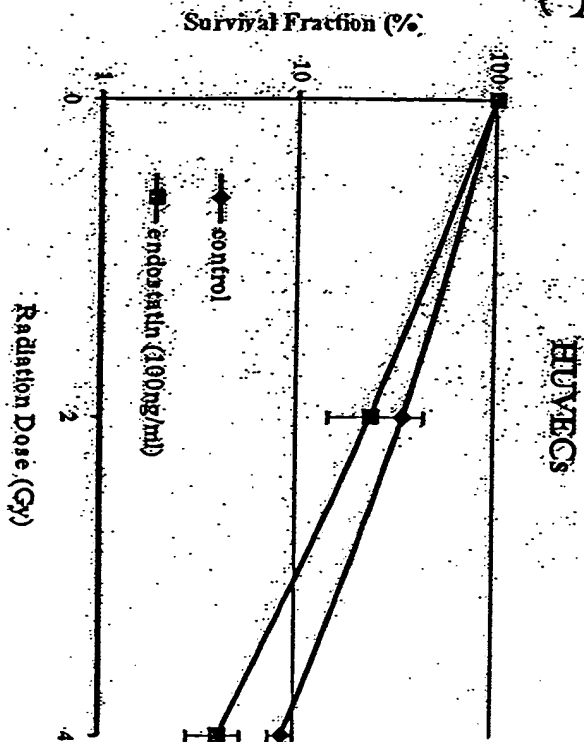


FIG. 59

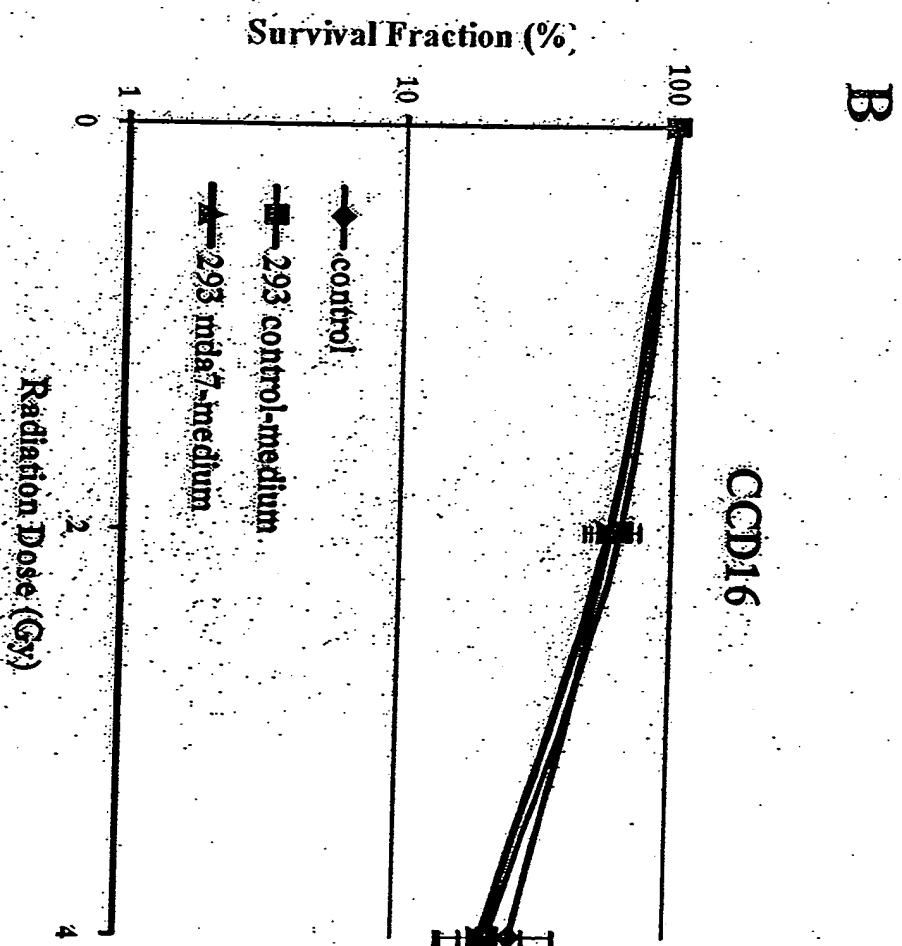
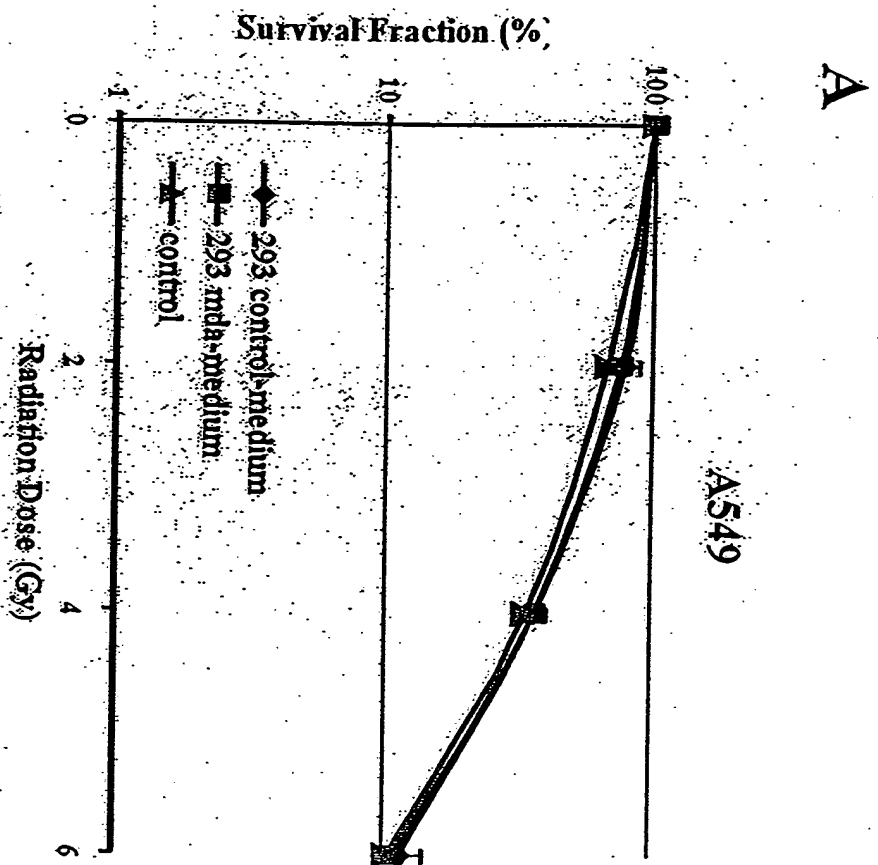


FIG. 60

Targeting Plasmid Constructs



FIG. 61

ER Targeting of MDA-7 Blocks Colony Formation

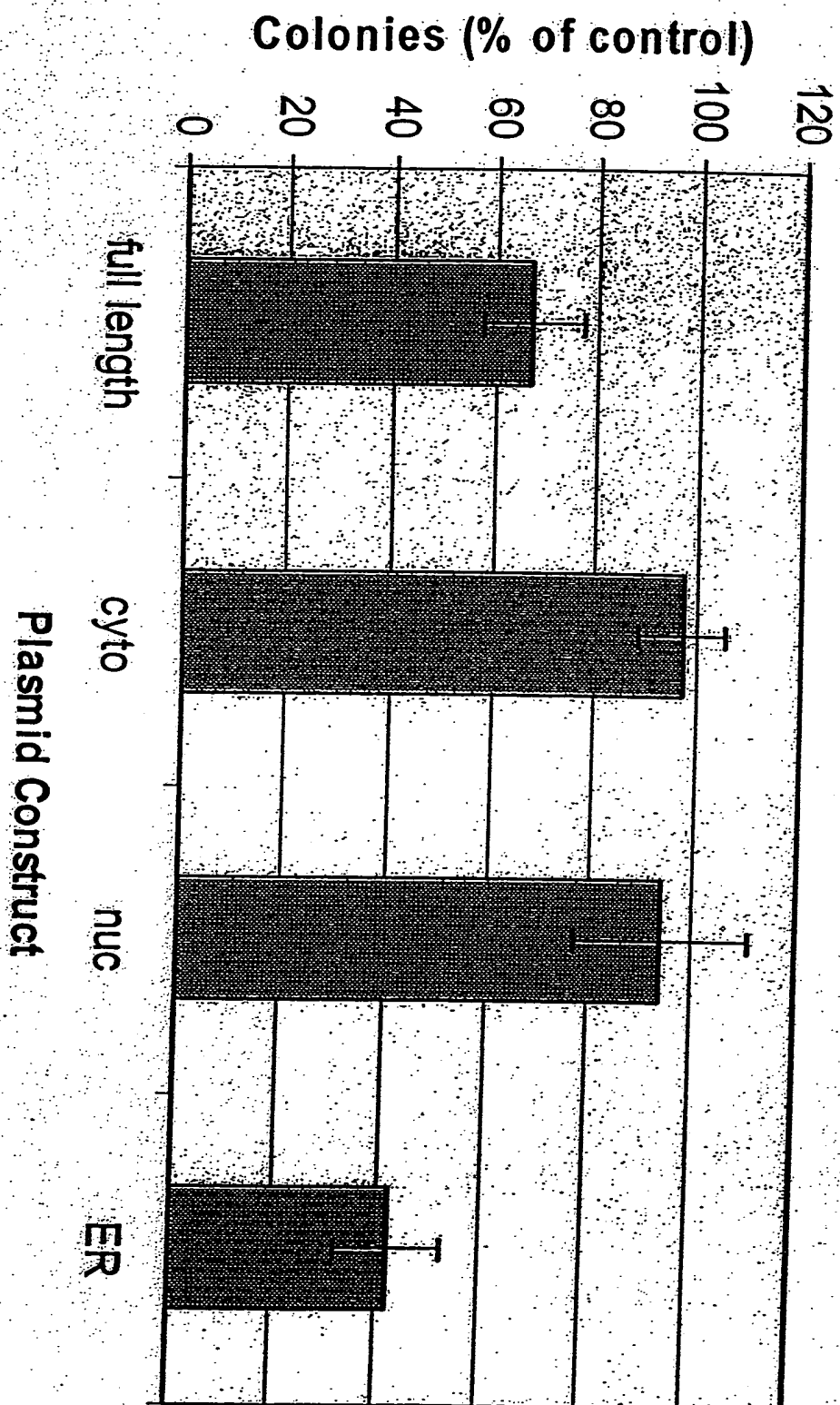


FIG. 62

ER-targeted MDA-7 is pro-apoptotic

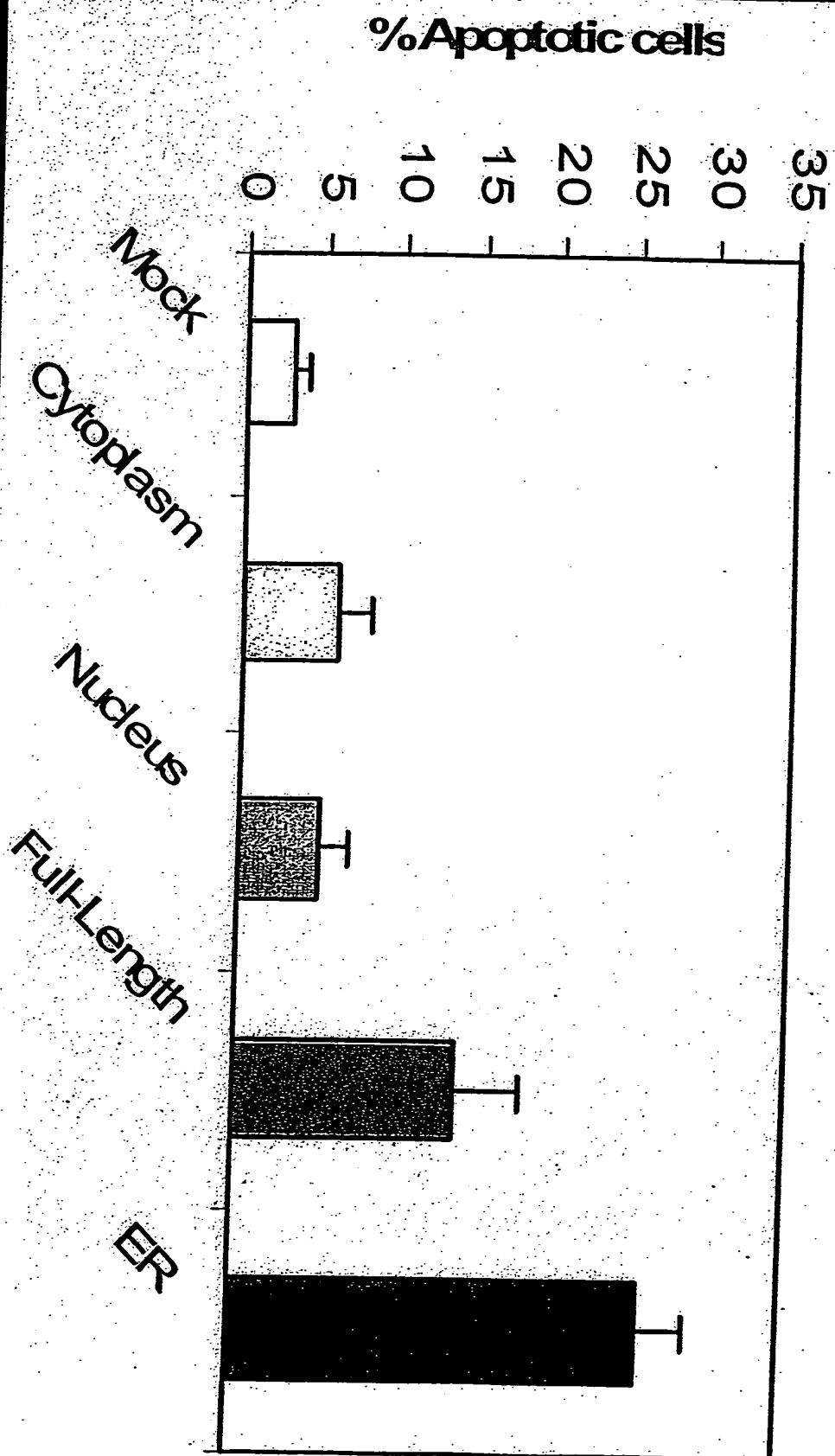


FIG. 63

Inhibition of human ovarian cancer cell proliferation by Ad-mdar7

MDAH 2774

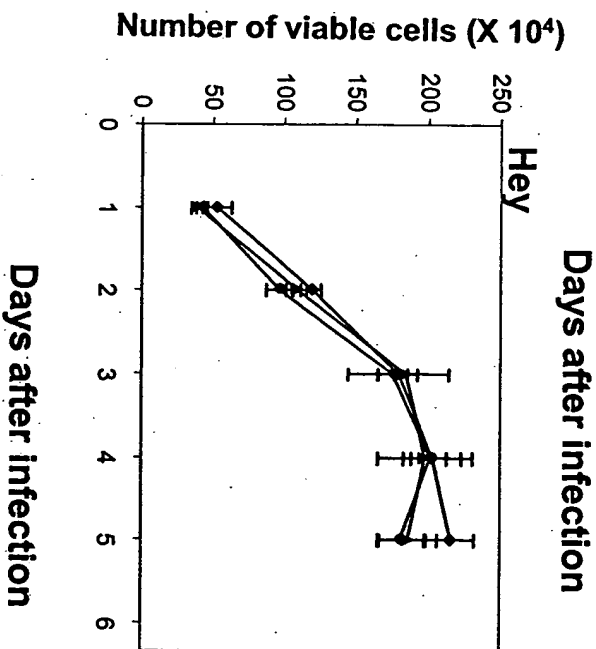
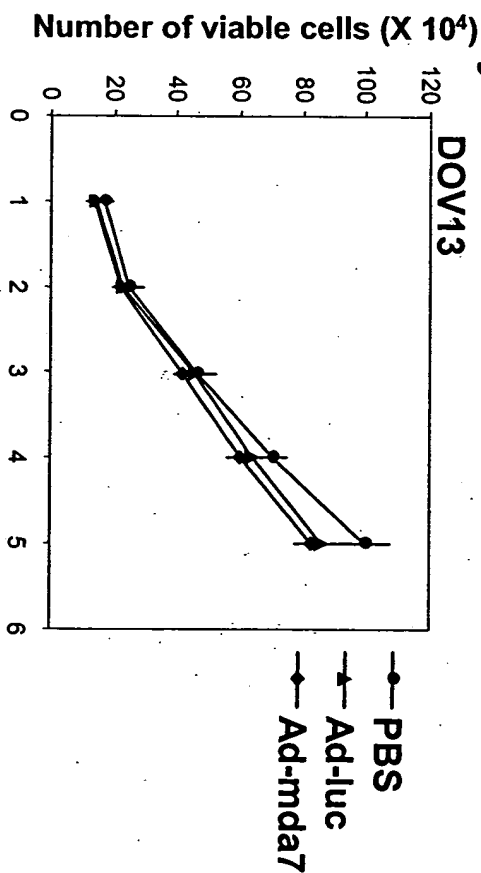
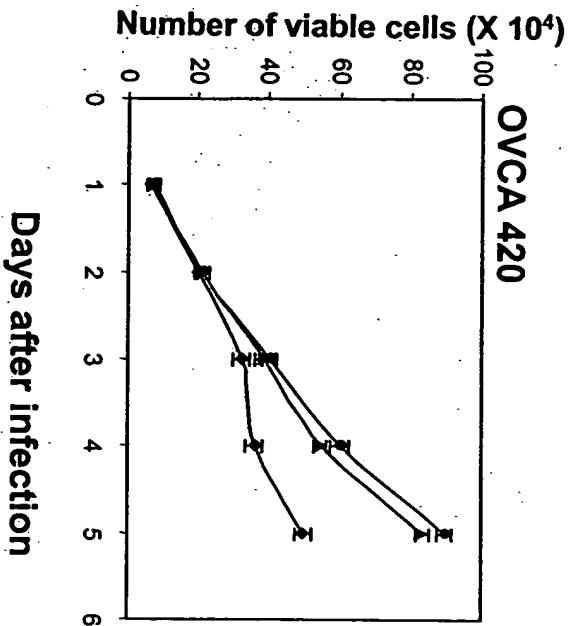
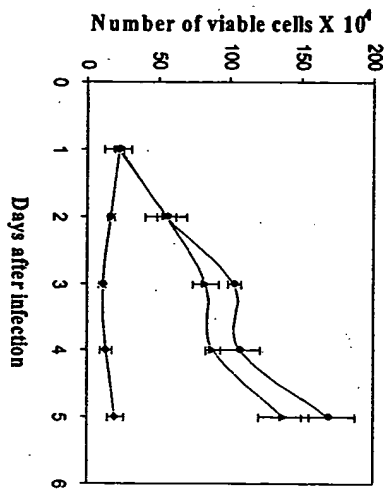


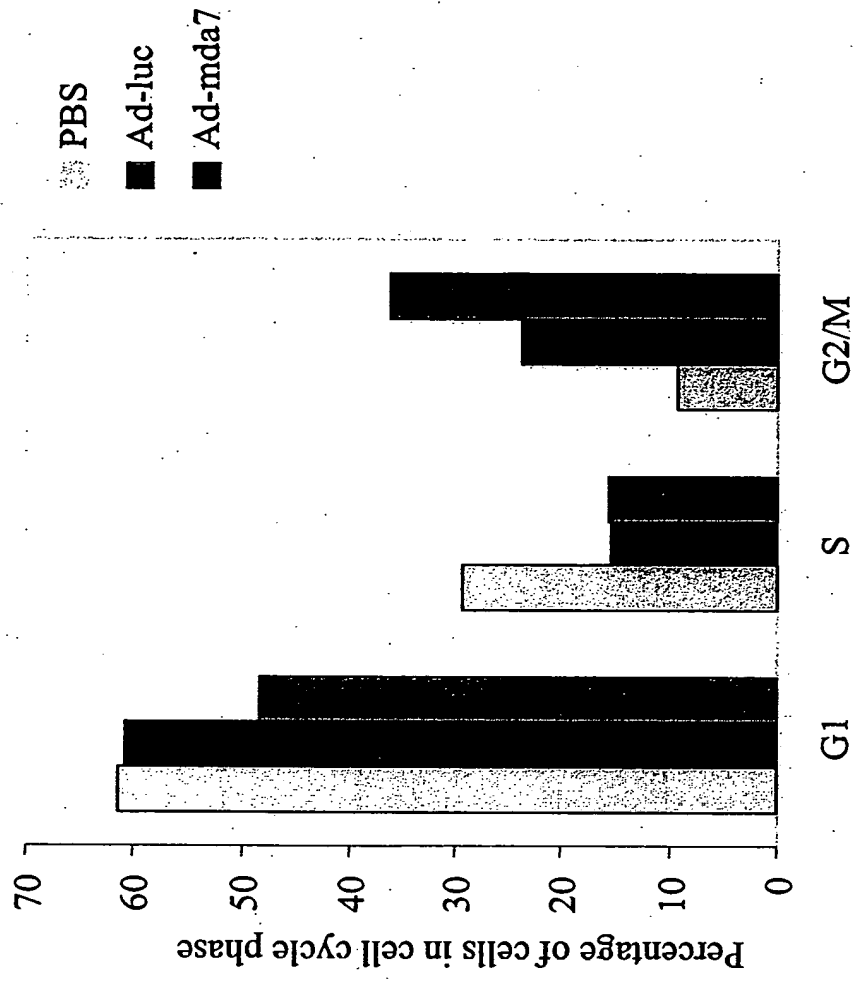
FIG. 64

Induction of cell cycle arrest by MDA-7 (MDAH 2774)

	G1	S	G2M	Apoptosis Sub G0
24 hrs PBS	30.55	34.55	34.9	2.05
Ad.Luc	32.95	36.6	30.45	1.41
Ad.mda-7	27.45	29.75	42.85	4
48 hrs PBS	40.8	32.6	26.6	0.955
Ad.Luc	28.75	32.45	38.8	0.84
Ad.mda-7	18.3	78	54.5	10.36

FIG. 65A

Ad-mda7 induced G2/M cell cycle arrest in OVCA 420



OVCA-420

FIG. 65B

Induction of apoptosis due to overexpression of MDA-7 (MDAH2774)

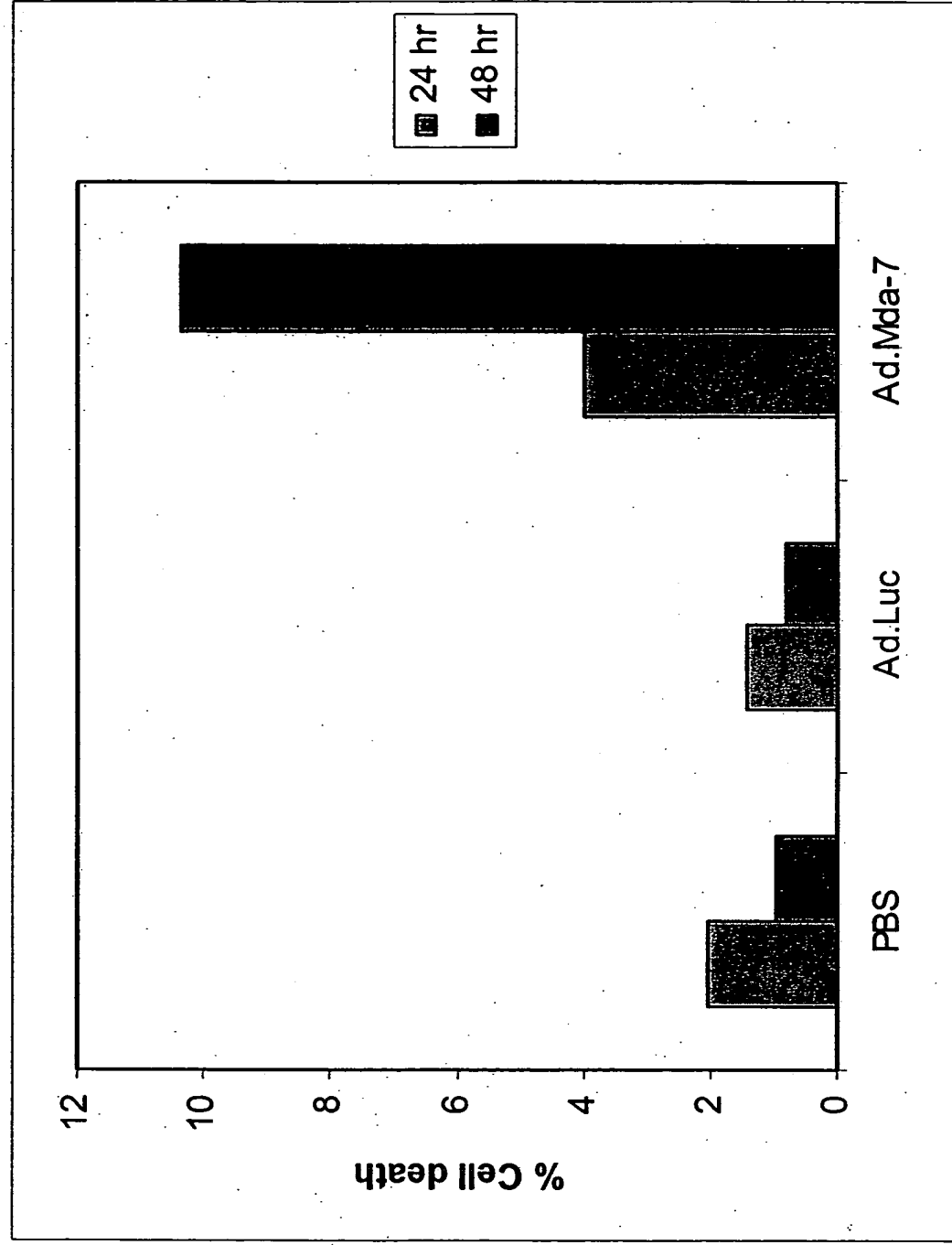


FIG. 66

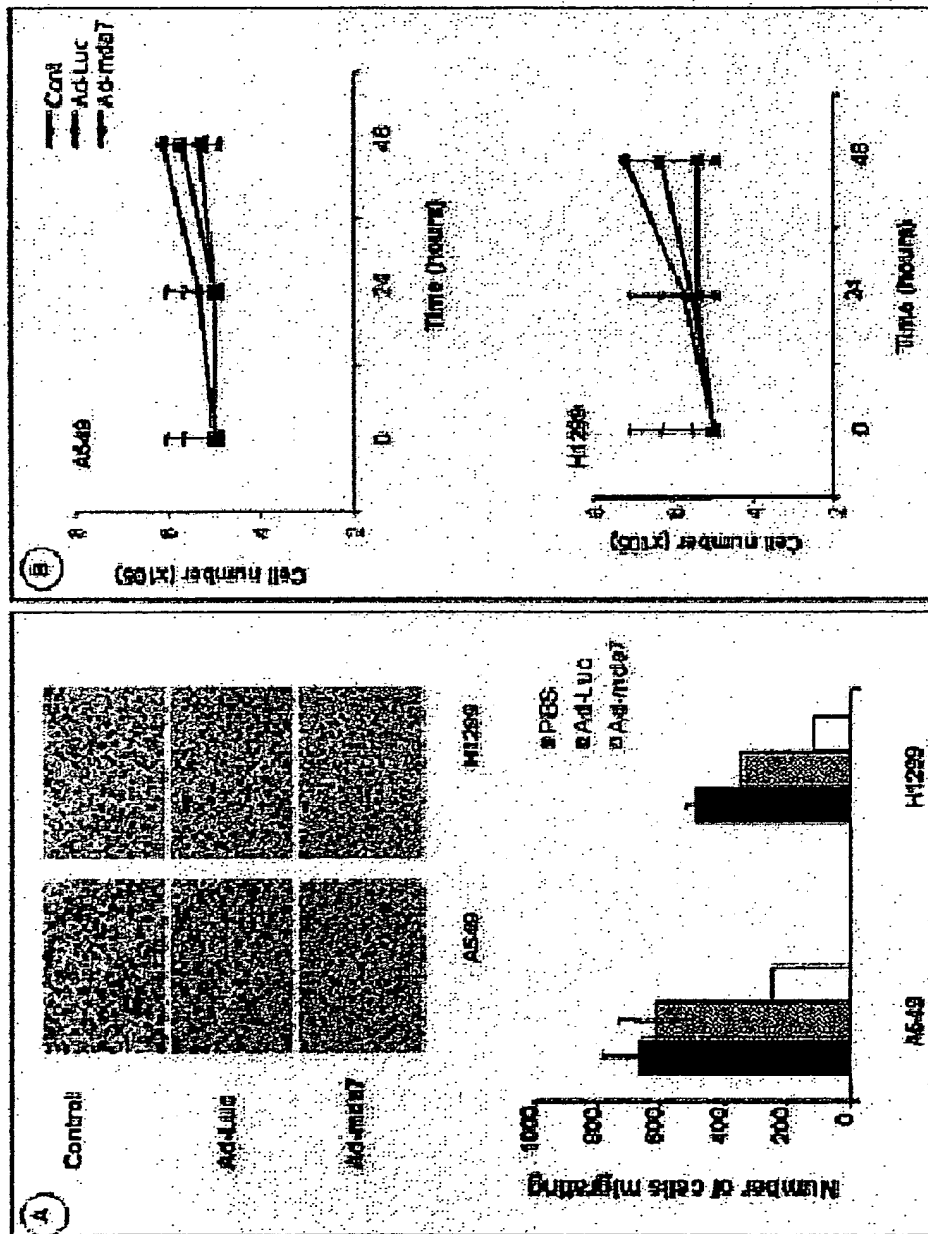


FIG. 67A-B

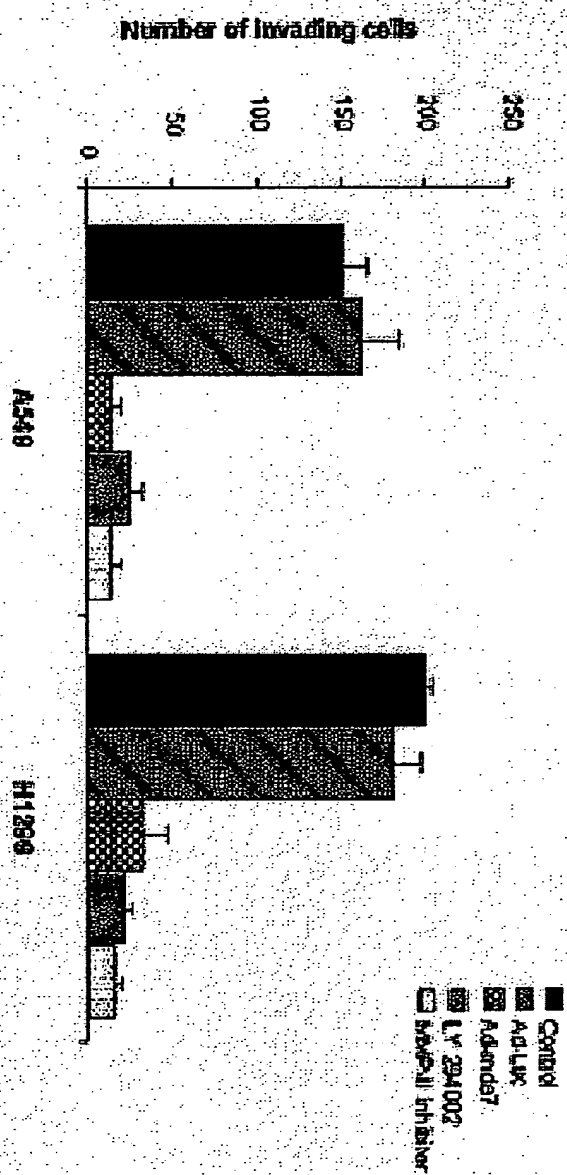


FIG. 68

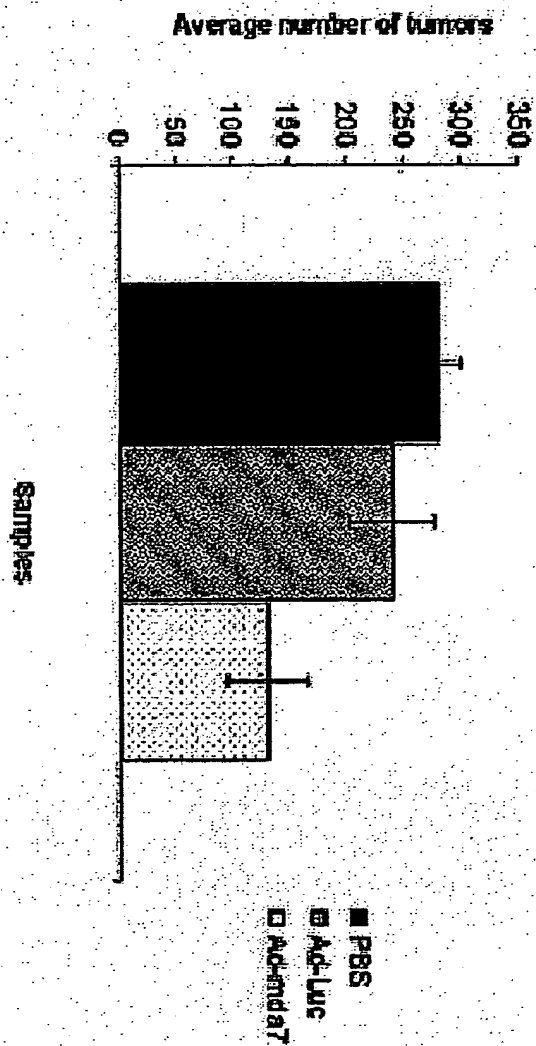


FIG. 69

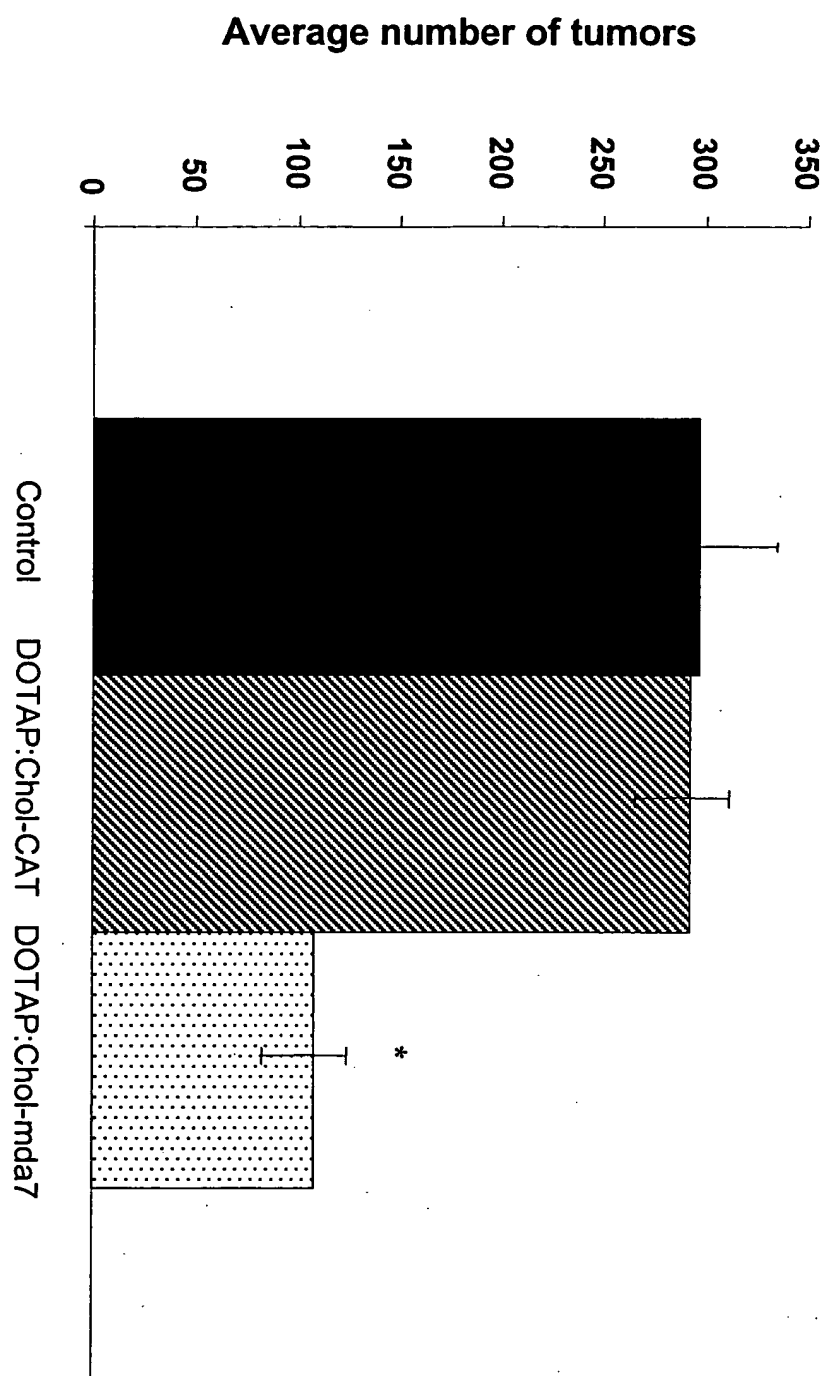


FIG. 70

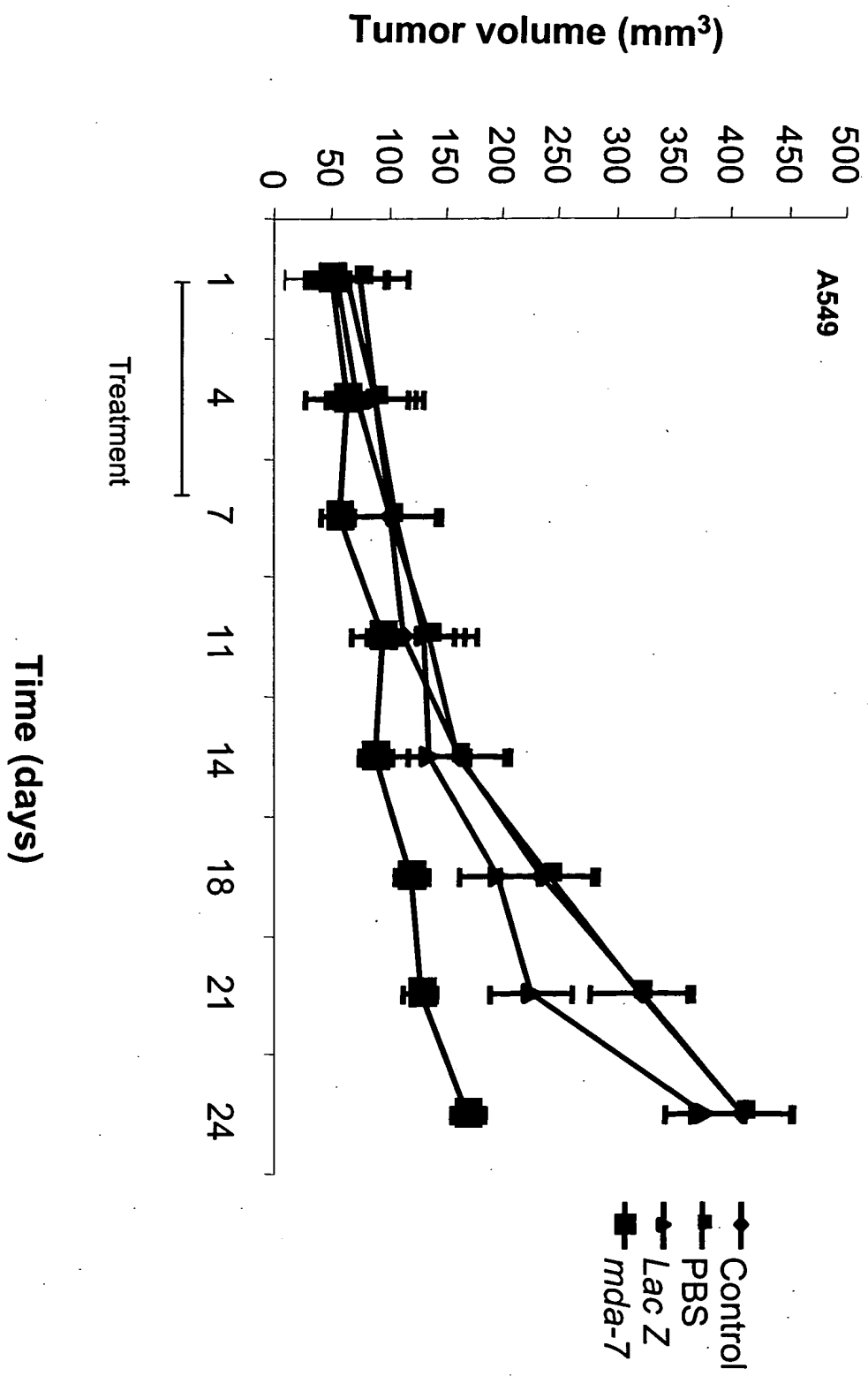


FIG. 71A

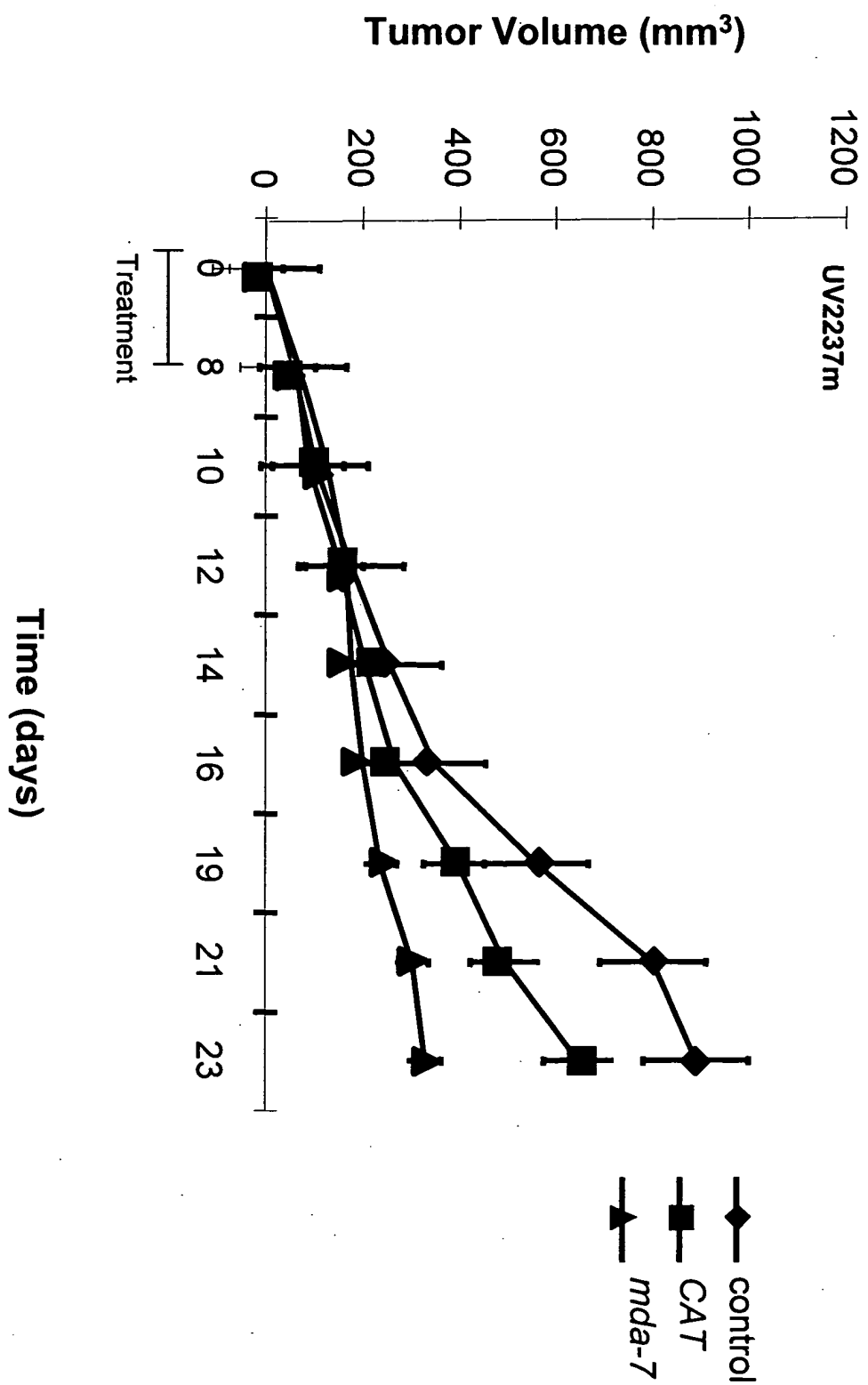


FIG. 71B

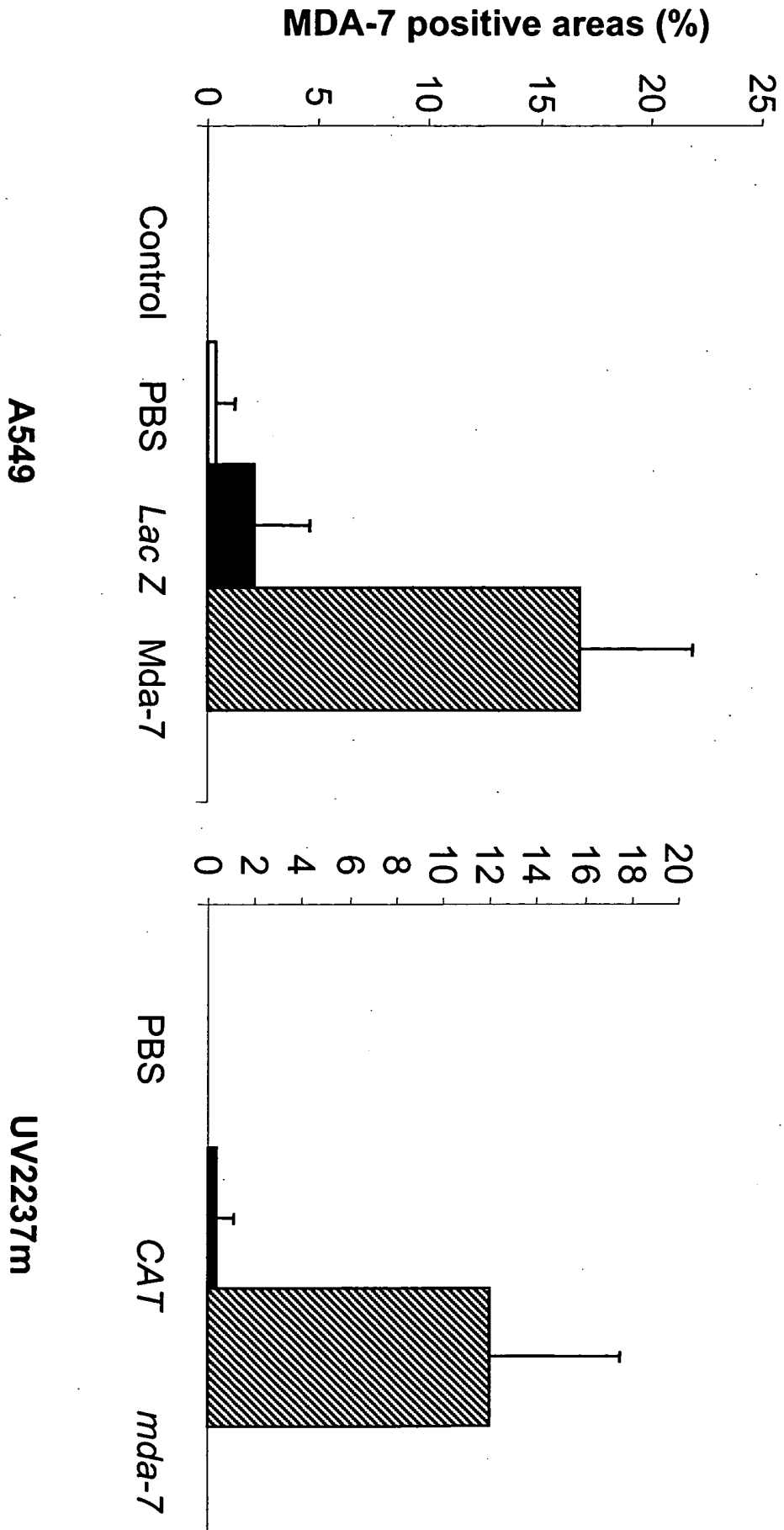


FIG. 71C

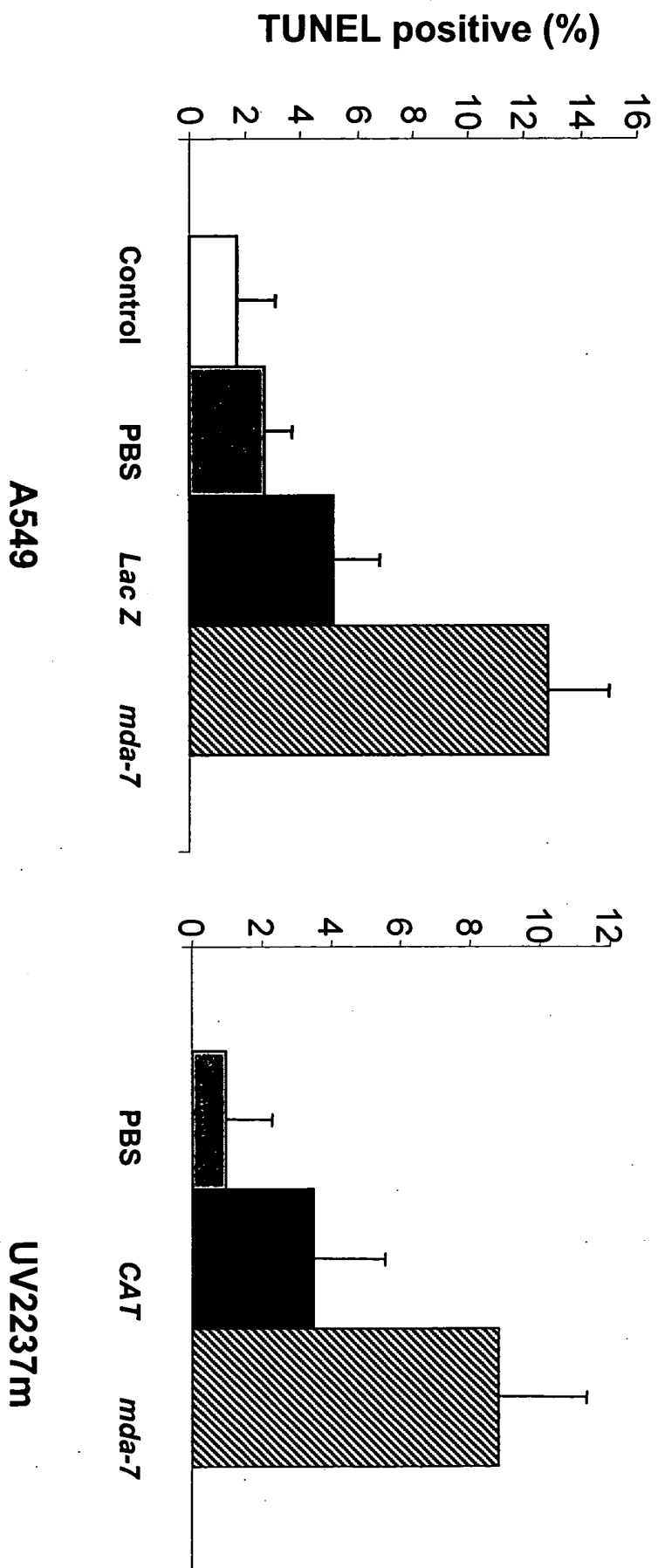


FIG. 72

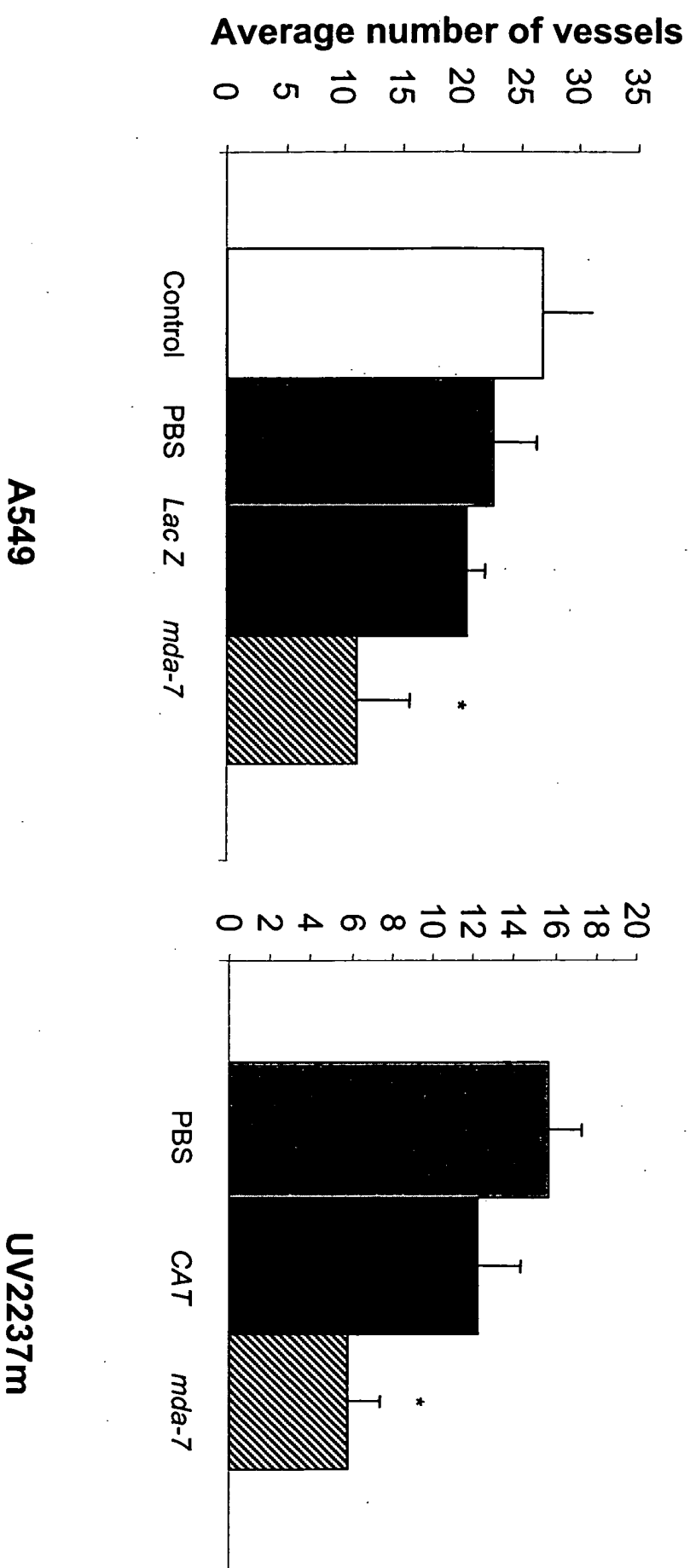


FIG. 73

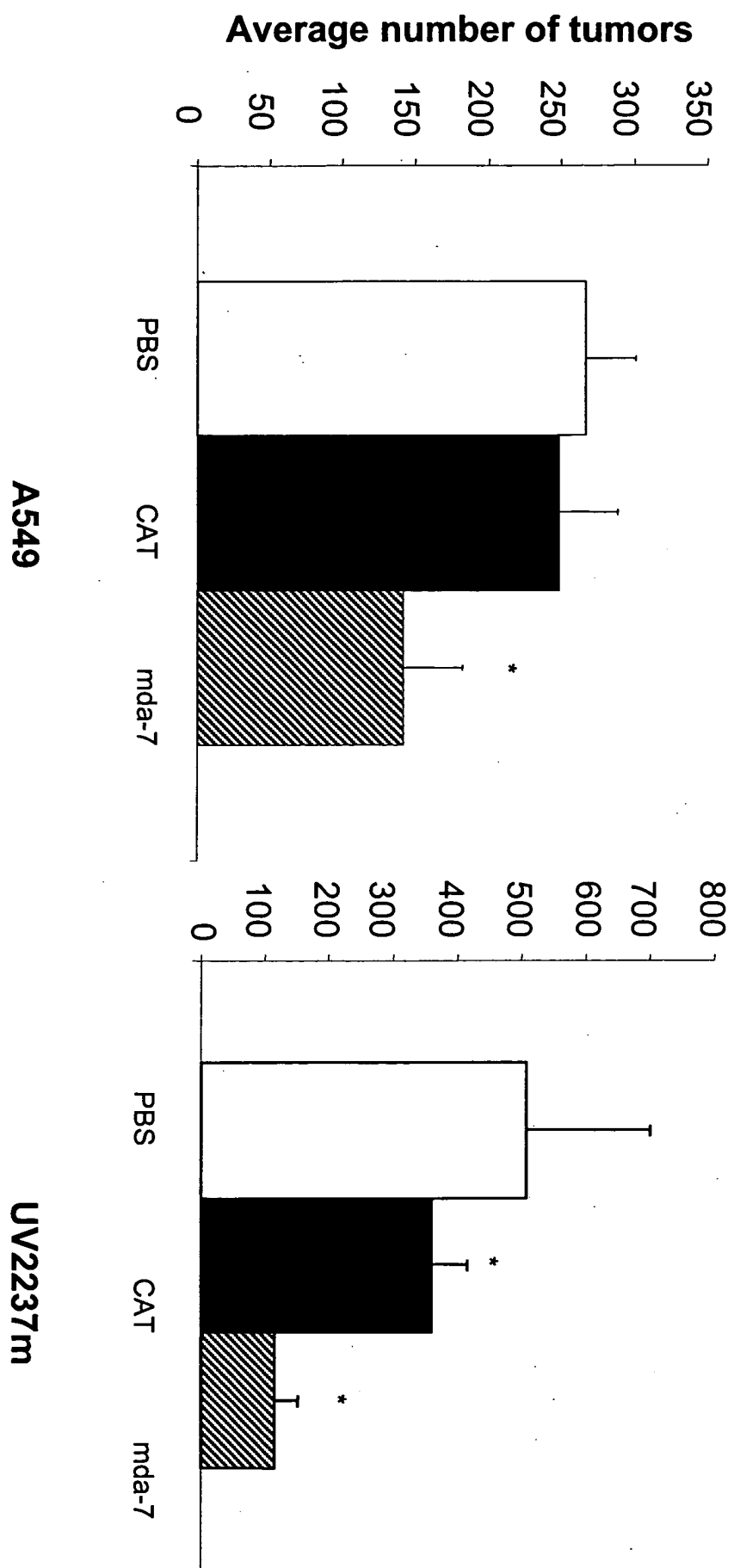


FIG. 74